VOLUME 111

JANUARY 15

1991

157 Dec 28 93 CUK-H01292-26-P02430 CM 26

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

• ORIGINAL ARTICLES

Presumed Ocular Histoplasmosis Syndrome
Thomas, Kaplan

Initial Surgery for Severe Proliferative Vitreoretinopathy
Lewis, Aaberg, Abrams

Repeat Surgery for Recurrent Proliferative Vitreoretinopathy
Lewis, Aaberg

Lattice Degeneration in Severe Myopia
Celorio, Pruett

Gyrate Atrophy
Wilson, Weleber, Green

Familial Exudative Vitreoretinopathy
van Nouhuys

Endoillumination and Retinal Injury
Kuhn, Morris, Massey

Light Damage in Detached Retina
Zilis, Machemer

Intraocular Pressure Control and Glaucomatous Damage
Mao, Stewart, Shields

Intraocular Pressure in Burned Patients
Evans

Perkins, Tono-Pen, and Schiötz Tonometry
Whitacre, Emig, Hassanein

Documenting Lens Opacities
Adamsons, Taylor, Enger, Taylor

Surgical Management of Oculomotor Nerve Palsy
Gottlob, Catalano, Reinecke

Echography and Carotid-Cavernous Sinus Fistulas
Spector

Low-Density Lipoprotein Receptors of Corneal Endothelium
Elner, Elner, Pavilack, Davis, Cornicelli, Yue

Corneal Ulceration in Nepal
Upadhyay, Karmacharya, Koirala, Tuladhar, Bryan, Smolin, Whitcher

• EDITORIAL

Hydroxyamphetamine. A Good Drug Lost?
Burde, Thompson

• LETTERS TO THE JOURNAL

Transesophageal echocardiography and mitral valve prolapse
Greven, Weaver, Harris, Watts, Slusher

Transesophageal echocardiography and mitral valve prolapse
Wiznia, Pearson

Follicular conjunctivitis and apraclonidine
Wilkerson, Lewis, Shields

Schirmer test with nasal stimulation
Tsubota

Discoid lupus erythematosus
Meiusi, Cameron, Holland, Summers

Hepatic cirrhosis and eyelid retraction
Bartley, Gorman

Flotation devices to facilitate amblyopia therapy
Hacker, O'Hara

Retinal pigment epitheliopathy in acute leukemia
Verbraak, van den Berg, Bos

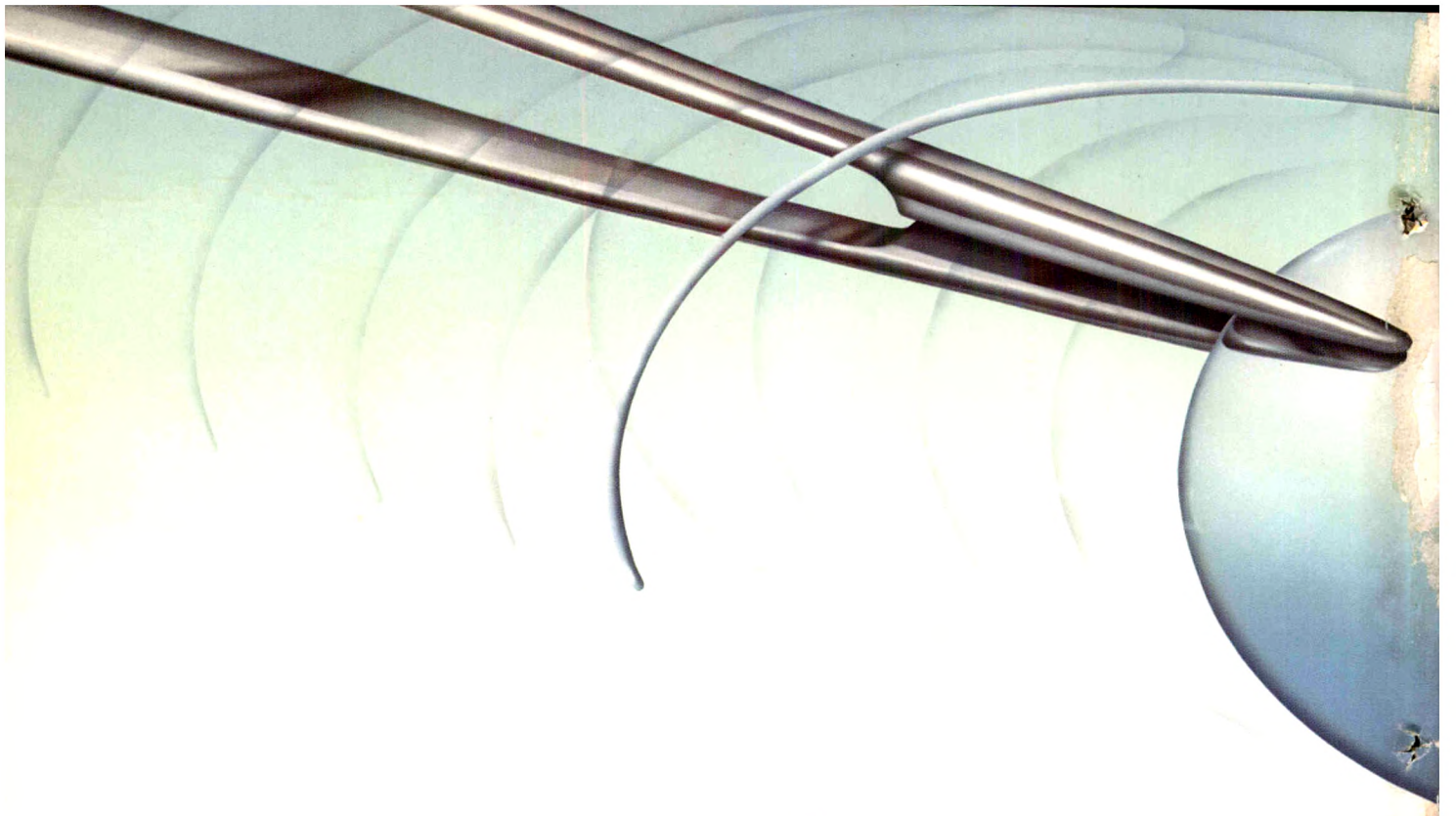
Metastatic renal cell carcinoma of the iris
Portnoy, Arffa, Johnson, Terner

Meibomian gland carcinoma
Bhalla, Vashisht, Gupta, Sen

Evisceration instrument
White, Hollsten

***Flavobacterium meningosepticum* keratitis**
Bucci, Holland

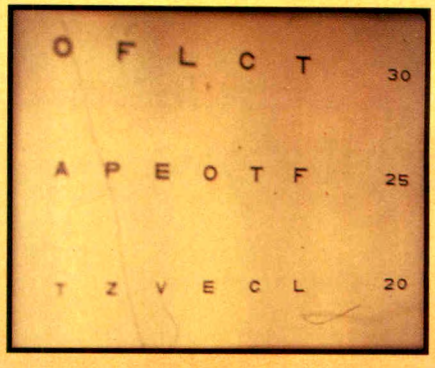
AIO®



Viscoelastic penetration this dynamic is the newest thing you'll notice

Have you memorized this?

P 24,327



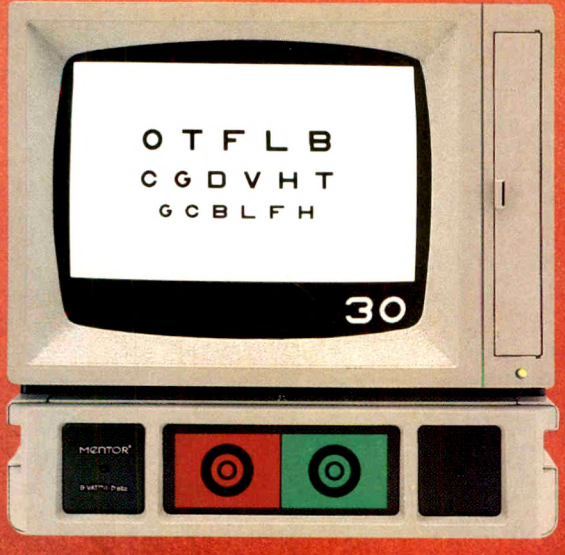
. . . so have your patients

Test their vision - not their memory

NEW

MENTOR® B-VAT™ II- ▷elta Video Acuity Tester

- **Randomized letter presentation**
- **Economical -** little more than the cost of some projectors. Performs basic tests and can be upgraded with corded LCD readout hand controller.
- **Convenience of *cordless* IR remote control**





- **Faster - less patient fatigue**
- **More accurate than projectors**
- **Versatile -** specialized tests built-in (contrast sensitivity); can be upgraded (binocular vision tests)

The B-VAT II- ▷elta is the newest member of the B-VAT II **family**:

B-VAT II - advanced testing capabilities

B-VAT II-SG - adds sinusoidal gratings for contrast sensitivity tests

BVS™ BINOCULAR VISION SYSTEM - stereo acuity testing capacity in an upgrade for any B-VAT II unit

MENTOR O&O INC.

3000 Longwater Drive, Norwell, MA 02061-1610

1-800-992-7557

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 January 1991 Series 3, Vol. 111, No. 1

TABLE OF CONTENTS

ORIGINAL ARTICLES

Surgical removal of subfoveal neovascularization in the presumed ocular histoplasmosis syndrome
Matthew A. Thomas and Henry J. Kaplan 1

Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy
Hilel Lewis, Thomas M. Aaberg, and Gary W. Abrams 8

Causes of failure after repeat vitreoretinal surgery for recurrent proliferative vitreoretinopathy
Hilel Lewis and Thomas M. Aaberg 15

Prevalence of lattice degeneration and its relation to axial length in severe myopia
José M. Celorio and Ronald C. Pruett 20

Ocular clinicopathologic study of gyrate atrophy
David J. Wilson, Richard G. Weleber, and W. Richard Green 24

Signs, complications, and platelet aggregation in familial exudative vitreoretinopathy
C. Erik van Nouhuys 34

Photic retinal injury from endoillumination during vitrectomy
Ferenc Kuhn, Robert Morris, and Michael Massey . . . 42

Light damage in detached retina
John D. Zilis and Robert Machemer 47

Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma
Lisa Kay Mao, William C. Stewart, and M. Bruce Shields 51

Increased intraocular pressure in severely burned patients
Lawrence S. Evans 56

The effect of Perkins, Tono-Pen, and Schiötz tonometry on intraocular pressure
Marc M. Whitacre, Mark Emig, and Khatab Hassanein 59

A new method for documenting lens opacities
I. Adamsons, K. I. Taylor, C. Enger, and H. R. Taylor 65

Surgical management of oculomotor nerve palsy
Irene Gottlob, Robert A. Catalano, and Robert D. Reinecke 71

Echographic diagnosis of dural carotid-cavernous sinus fistulas
Robert H. Spector 77

Human and monkey corneal endothelium expression of low-density lipoprotein receptors
Susan G. Elner, Victor M. Elner, Mark A. Pavilack, Harry R. Davis, Joseph A. Cornicelli, and Beatrice Y. J. T. Yue 84

Epidemiologic characteristics, predisposing factors, and etiologic diagnosis of corneal ulceration in Nepal
Madan P. Upadhyay, Purna C. D. Karmacharya, Shasank Koirala, Nhuchhe R. Tuladhar, Larry E. Bryan, Gilbert Smolin, and John P. Whitcher 92

EDITORIAL

Hydroxyamphetamine. A good drug lost?
Ronald M. Burde and H. Stanley Thompson 100

LETTERS TO THE JOURNAL

Transesophageal echocardiography for detecting mitral valve prolapse with retinal artery occlusions. *Craig M. Greven, Richard G. Weaver, William R. Harris, L. Earl Watts, and M. Madison Slusher,* **103. Use of transesophageal echocardiography for detection of a likely source of embolization to the central retinal artery.** *Robert A. Wiznia and W. Neil Pearson,* **104. Follicular conjunctivitis associated with apraclonidine.** *Mark Wilkerson, Richard A. Lewis, and M. Bruce Shields,* **105. The importance of the Schirmer test with nasal stimulation.** *Kazuo Tsubota,* **106. Discoid lupus erythematosus of the eyelid complicated by wound dehiscence.** *Rhondi S. Meiusi, J. Douglas Cameron, Edward J. Holland, and C. Gail Summers,* **108. Hepatic cirrhosis as a doubtful cause of eyelid retraction.** *George B. Bartley and Colum A. Gorman,* **109. Flotation devices to facilitate amblyopia therapy.** *Henry D. Hacker and Mary O'Hara,* **110. Retinal pigment epitheliopathy in acute leukemia.** *Frank D. Verbraak, Wouter van den Berg, and Pierre J. M. Bos,* **111. Metastatic renal cell carcinoma of the iris manifesting as an intrastromal iris cyst.** *Scott L. Portnoy, Robert C. Arffa, Bruce L. Johnson, and Irwin S. Terner,* **113. Meibomian gland carcinoma in a 20-year-old patient.** *Jatinder S. Bhalla, S. Vashisht, Vijay K. Gupta, and A. K. Sen,* **114. A new instrument for use in evisceration.** *William L. White and Donald A. Hollsten,* **115. *Flavobacterium meningosepticum* keratitis successfully treated with topical trimethoprim-sulfamethoxazole.** *Frank A. Bucci, Jr., and Edward J. Holland,* **116.**

CORRESPONDENCE

***Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy.** *Steven A. Teich, Marc Rosenblatt, and Alan Friedman,* **118. Reply.** *Pravin U. Dugel, Narsing A. Rao, David J. Forster, Lawrence P. Chong, George T. Frangieh, Fred Sattler, and*

(Table of Contents continued on Advertising Page 8)





Tears Renewed Ointment™ is Free

Free of Lanolin and Preservatives and Free to You When You Call 1-800-535-7155

Lanolin, obtained from the wool of sheep, and the harsh chemicals in preservatives can cause irritation to someone suffering with dry eye syndrome.

Tears Renewed Ointment™ is dry eye relief. Free of ingredients that can be uncomfortable for your patient.

And priced to save your patient money.

Call today for your free samples.



DIAGNOSE THE PROBLEM.



PRESCRIBE THE RELIEF.



Akorn, Inc.

1-800-535-7155

In Louisiana 1-800-344-2291

100 Akorn Dr. • Abita Springs, LA 70420

Akorn's products are priced to save you money

WE OFFER AN EXTENSIVE LINE OF DIAGNOSTIC AND THERAPEUTIC PRODUCTS.

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 January 1991 Series 3, Vol. 111, No. 1

TABLE OF CONTENTS *(continued from Advertising page 6)*

John A. Lopresti, **118. The gradient filter test to assess amblyopia.** *Marco Nardi,* **119. Reply.** *Ronald V. Keech and Pamela J. Kutschke,* **120. Vitrectomy retinotomy aspiration biopsy of choroidal tumors.** *Gholam A. Peyman,* **121. Reply.** *David M. Fastenberg, Paul T. Finger, Quintus Chess, Samuel Packer, and June H. Koizumi,* **121.**

BOOK REVIEWS

Thyroid Eye Disease, ed. 2 (Devron H. Char). *Reviewed by Joel Weinstein,* **122. Normal Pressure Glaucomas (Alain Bechetoille).** *Reviewed by Pierre Blondeau,* **122. Vom Helmholtz-Augenspiegel zur Funduskamera (Alfred Schett), 122. Year Book of Ophthalmology 1990 (Edited by Peter R. Laibson), 123.**

ABSTRACTS 124

NEWS ITEMS 131

CLASSIFIEDS . . . . . Begins on Advertising 42

COPYRIGHT TRANSFER . . . . . Advertising 33

INSTRUCTIONS TO AUTHORS . . . . . Advertising 27

PRODUCTS AND SERVICES . . . . . Begins on Advertising 34

ADVERTISING INDEX . . . . . Advertising 45

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

LINDA G. CLAUSEN
Records Manager

KAREN D. JOHNSON
Manuscript Editor

MOLLY MELICK
Assistant to the Editor

DIANN J. MARQUIS
Editorial Assistant

MICHAEL J. LUND
Subscription Correspondent

LYNN ANN LINDVIG
AND
RENEE L. KASTAR
Sales and Production

Surgical Removal of Subfoveal Neovascularization in the Presumed Ocular Histoplasmosis Syndrome

Matthew A. Thomas, M.D., and Henry J. Kaplan, M.D.

We treated two patients with presumed ocular histoplasmosis, subfoveal neovascular membranes, and progressive visual acuity loss to 20/400. Vitreoretinal surgical techniques were used to remove the subfoveal membranes. Visual acuity returned to 20/20 with seven months of follow-up in one patient (Case 1) and to 20/40 with three months of follow-up in the other patient (Case 2). No evidence of persistent or recurrent subretinal neovascular membranes in either patient have been noted. These preliminary results suggest that vitreoretinal surgical techniques may be successful in mechanically removing subfoveal neovascular membranes with preservation of overlying neurosensory retina and thus preservation of central visual acuity.

THE MACULAR PHOTOCOAGULATION STUDY has proven laser therapy to be effective for extrafoveal neovascularization (200 to 2,500 μm from the center of the foveal avascular zone) secondary to presumed ocular histoplasmosis.[1] Furthermore, laser therapy has proven to be effective for juxtafoveal subretinal neovascularization (1 to 199 μm from the center of the foveal avascular zone) in eyes with presumed ocular histoplasmosis and idiopathic disease but only in association with normotensive age-related macular degeneration.[2-4] The Macular Photocoagulation Study Group initiated a pilot study of laser therapy of subfoveal neovascularization, which complicated the presumed ocular histoplasmosis syndrome. The preservation or recovery of lost central vision, however, is not expected with this modality of treatment. Currently, laser therapy is not advised routinely for subfoveal neovascular membranes in presumed ocular histoplasmosis. Given the generally poor natural course of subfoveal neovascular membranes in presumed ocular histoplasmosis, we undertook a surgical approach to remove the membrane with the objective of preserving the potential for central vision.

Accepted for publication Oct. 25, 1990.

From Retina Consultants, Ltd., St. Louis, Missouri (Dr. Thomas), and Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri (Dr. Kaplan). This study was supported in part by a grant from the Retina Research & Development Foundation (Retina Consultants, Ltd.) and an unrestricted grant from Research to Prevent Blindness, Inc. (Department of Ophthalmology and Visual Sciences, Washington University School of Medicine).

Reprint requests to Matthew A. Thomas, M.D., Retina Consultants, Ltd., Ste. 17413, One Barnes Hospital Plaza, St. Louis, MO 63110.

Patients and Methods

Patients with fundus findings of the presumed ocular histoplasmosis syndrome with subfoveal neovascularization, in whom the visual prognosis was believed to be extremely poor, were identified. Treatment options, including observation, laser ablation of the neovascular membrane and overlying fovea, and neovascular membrane excision, were discussed in detail and informed consent was obtained from the patient for surgery.

Best-corrected visual acuity was determined for each eye separately. Fundus photographs and a recent (within 72 hours of surgery) fluorescein angiogram were obtained.

On a screen in the operating room, we projected an arteriovenous phase frame from the recent angiogram. The projected image was reversed and inverted to match the surgeon's view through the microscope, and fundus landmarks were identified carefully. After a pars plana vitrectomy, a retinotomy site was selected outside the fovea adjacent to the leading edge of the neovascular membrane. The retina was cauterized lightly with the tapered 20-gauge endodiathermy probe. A small, full-thickness hole in whitened neurosensory retina was then made with the myringotomy blade. A 30-gauge blunt tip needle was introduced into the retinotomy, and gentle infusion of balanced salt solution created a limited neurosensory

detachment overlying the membrane, retinal pigment epithelium, and Bruch's membrane. This separation allowed manipulation with picks and forceps in the subretinal space while minimizing trauma to neurosensory retina. Since the retinotomy was eccentric to the fovea, the shaft of the pick or forceps was used to push the elevated retina until the instrument reached the subfoveal neovascular membrane. The instrument tip could be visualized through neurosensory retina.

Picks with an angle greater than 90 degrees (such as the Olk 130-degree pick) facilitated manipulation of the membrane without striking retinal pigment epithelium or Bruch's membrane with the heel of the instrument. The pick was used to separate the membrane from adjacent retinal pigment epithelium or neurosensory retina. Angled forceps (such as the de Juan forceps) allowed reaching under the neurosensory retina to grasp the membrane.

To minimize the risk of hemorrhage when the membrane was avulsed from its choriocapillaris connection, we increased intraocular pressure transiently by raising the infusion bottles. No significant bleeding was encountered. Once the membrane was dislodged or dissected free, it was grasped with the forceps and removed through the pars plana sclerotomy. An air-fluid exchange was then performed, and light endophotocoagulation burns were placed around the retinotomy, sparing foveal retina. Sulfur hexafluoride or perfluoropropane gas was left in the eye to tamponade the retinotomy.

Case Reports

Case 1

A 42-year-old woman had a five-day history of metamorphopsia in her left eye. Visual acuity was R.E.: 20/20 and L.E.: 20/60−2 with a neurosensory detachment involving the fovea and subretinal blood eccentric to the fovea in the left eye (Fig. 1). Both eyes had chorioretinal lesions consistent with the presumed ocular histoplasmosis syndrome. Fluorescein angiography confirmed an extrafoveal membrane, and the patient underwent argon green photocoagulation (Fig. 2). Within six weeks the subretinal blood and neurosensory detachment cleared and visual acuity improved to 20/25−3. Fluorescein angiography showed obliteration of the subretinal neovascular membrane.

The patient returned two months later with a central scotoma in the left eye with visual acuity of 20/400 eccentrically (Fig. 3). Fluorescein angiography demonstrated a subfoveal recurrence of the neovascular membrane (Fig. 4). Visual acuity remained at the 20/200 to 20/400 level during six weeks of observation.

In this patient, the retinotomy was made inferotemporal to the fovea on the edge of the



Fig. 1 (Thomas and Kaplan). Case 1. Visual acuity reduced to 20/60−2 by an extrafoveal subretinal neovascular membrane with a neurosensory detachment involving the fovea.

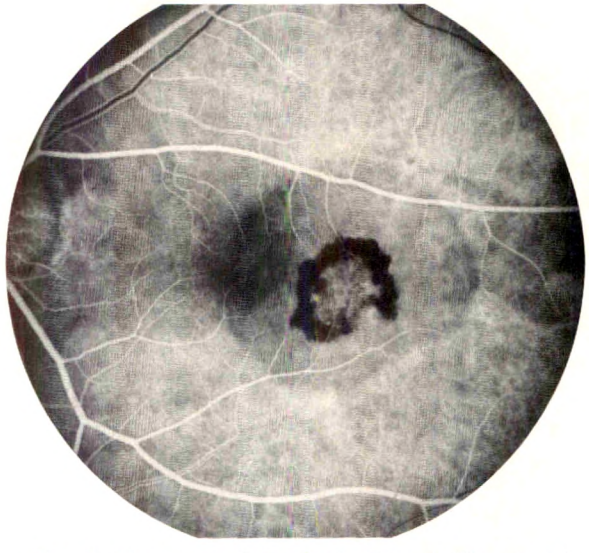


Fig. 2 (Thomas and Kaplan). Case 1. Fluorescein angiogram of the extrafoveal subretinal neovascular membrane before photocoagulation.



Fig. 3 (Thomas and Kaplan). Case 1. Recurrent neovascular membrane emanating from the edge of the previous photocoagulation scar has extended beneath the fovea and reduced visual acuity to 20/400.

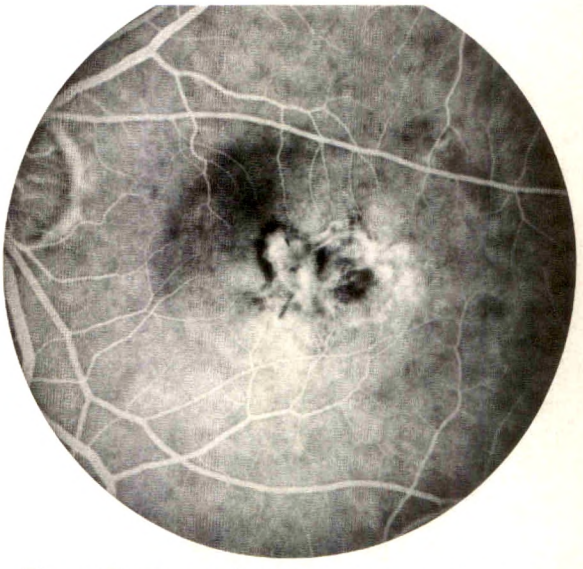


Fig. 4 (Thomas and Kaplan). Case 1. Fluorescein angiogram of neovascular membrane demonstrates progression beneath the fovea.

previous laser scar. As we expected, the neurosensory retina remained adherent to the Bruch's–retinal pigment epithelium complex at the site of the previous photocoagulation. After the myringotomy blade was used to create a full-thickness hole in diathermized retina, vertical intraocular scissors were used to enlarge



Fig. 5 (Thomas and Kaplan). Case 1. Ten weeks after surgical removal of the subretinal neovascular membrane. Visual acuity improved to 20/25−3. The retinal pigment epithelial defect beneath the fovea has been partially covered by migration, proliferation, or both from adjacent retinal pigment epithelium.

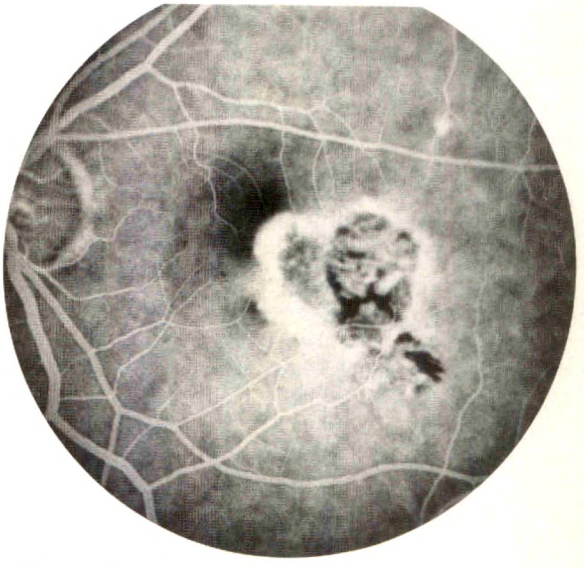


Fig. 6 (Thomas and Kaplan). Case 1. The fluorescein angiogram ten weeks postoperatively shows staining of the retinal pigment epithelium in the fovea and around the retinotomy and laser scars. No subretinal neovascularization is seen.

the hole slightly. (We subsequently found such enlargement to be unnecessary.) A spatula pick was used to dislodge this neovascular membrane from surrounding retinal pigment epithelium and underlying Bruch's membrane with minimal force. The membrane tilted on edge and was easily grasped with forceps. Since the eye was phakic, 20% sulfur hexafluoride gas was used for intraocular tamponade.

At one week postoperatively, pinhole visual acuity was 20/200 in the left eye with no apparent recurrence of the membrane. By one month postoperatively, a halo in the retinal pigment epithelium corresponding to the area of intraoperative neurosensory detachment was noted. The retina was thickened around the retinotomy but remained attached.

Ten weeks postoperatively, visual acuity improved to 20/25−3 (Fig. 5). By three months, visual acuity improved to 20/20 and remained at this level with follow-up of seven months since the operation. Repeat fluorescein angiography confirmed staining of the retinal pigment epithelium, but neither recurrence nor persistence of subretinal neovascularization has occurred (Fig. 6).

Case 2

A 42-year-old man had a two- to three-week history of blurring and metamorphopsia in the right eye. Visual acuity was R.E.: 20/25 and L.E.: 20/20. Minimal peripapillary retinal pigment epithelial atrophy was seen, and peripheral lesions consistent with presumed ocular histoplasmosis syndrome were observed. Punctate flecks of blood lay beneath the center of the right fovea; fluorescein angiography confirmed a subfoveal neovascular membrane. Given the good visual acuity, no laser therapy was advised. Oral prednisone was used without effect.

Over the ensuing three months, visual acuity declined in the right eye to 20/400. A neurosensory retinal detachment developed, and subretinal blood increased in the right macula overlying the enlarging neovascular membrane (Figs. 7 and 8). The patient underwent surgical excision of the membrane approximately four months after the onset of symptoms.

In this patient, the retinotomy was placed approximately 1 mm superior to the fovea. The spatula pick was used in an unsuccessful attempt to dislodge the edge of the subretinal neovascular membrane. The edge of the membrane, however, could be discerned and was grasped with the pick forceps. Three attempts at grasping the membrane were made without success. Finally, the membrane was successfully grasped and came free with gentle traction. The membrane separated from the adjacent retinal pigment epithelium with only a small rim of retinal pigment epithelium adherent to the membrane. The diode endolaser was used to create retinal burns around the edge of the retinotomy, and a total air-fluid exchange was performed. Sulfur hexafluoride gas (20%) was left in the eye at the conclusion of the procedure.

During the first four weeks postoperatively, the neurosensory macular detachment persisted, and visual acuity remained 20/200. By the fifth week, the retina flattened, all the remaining blood resorbed, and visual acuity improved to 20/50+2. Repeat fluorescein angiography disclosed hyperfluorescence at the edge of the retinotomy scar, as well as the disturbed retinal pigment epithelium in the fovea. No neovascular membrane persisted or recurred with three months of follow-up, and visual acuity improved to 20/40+1 (Figs. 9 and 10).

Results

Microscopic examination of the tissue in each case was similar (Fig. 11). The subfoveal neovascular membranes consisted of a basement-membrane matrix, proliferated retinal epithelial cells, endothelial cells, and capillaries.

Discussion

The classic triad of the presumed ocular histoplasmosis syndrome, as first described by Woods and Wahlen,[5] includes scars and hemorrhagic detachment of the macula, peripheral atrophic punched-out chorioretinal lesions (histo spots), and peripapillary chorioretinal scarring. Visual prognosis in patients with maculopathy is poor. Schlaegel[6] reported that one in 44 patients with a histoplasmosis scar in the macula had a chance of recurrence in the macula over the ensuing three years. If no scars were noted, however, the chances for the development of the maculopathy were reduced to one in 50 patients. In most patients, the maculopathy is caused by a subretinal neovascular membrane with an associated serous or hemorrhagic detachment of neurosensory retina that leads to severe visual impairment. The neovascular-



Fig. 7 (Thomas and Kaplan). Case 2. Subfoveal neovascular membrane with a serous neurosensory detachment and subretinal blood with visual acuity decreased to 20/400.

ization most frequently develops at the site of an old, healed chorioretinal scar. Although there are discontinuities of Bruch's membrane in the peripheral retinal lesions, for reasons

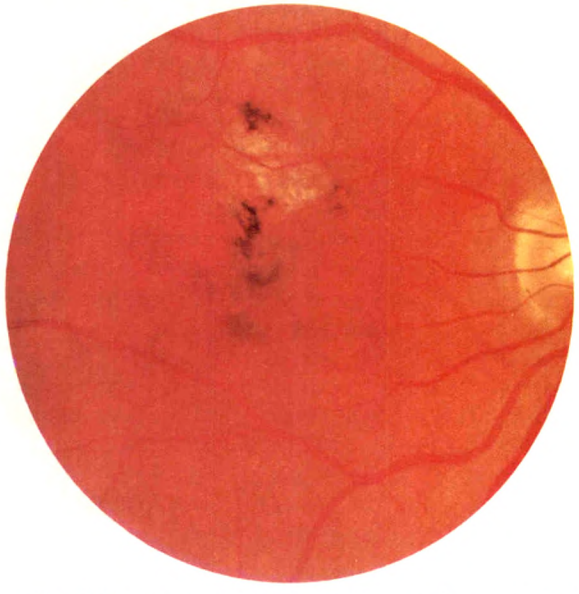


Fig. 9 (Thomas and Kaplan). Case 2. Two months after surgical removal of subfoveal neovascular membrane the retinal pigment epithelial defect is partially covered by adjacent cell migration, proliferation, or both.

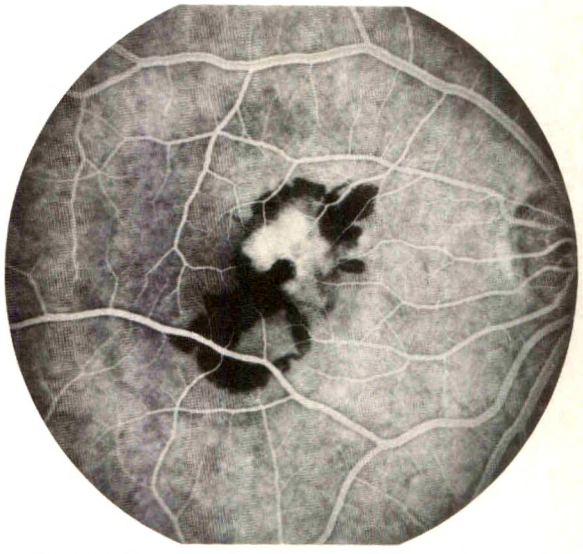


Fig. 8 (Thomas and Kaplan). Case 2. Fluorescein angiogram of subfoveal neovascular membrane present in Figure 7.

that remain unclear these are rarely associated with neovascularization and disciform scarring.[7]

In any patient with presumed ocular histoplasmosis and subfoveal neovascularization, the anticipated natural progression of the disease as well as the risks and benefits of laser or surgical intervention must be carefully considered. Although most patients who develop macular subretinal neovascular membranes

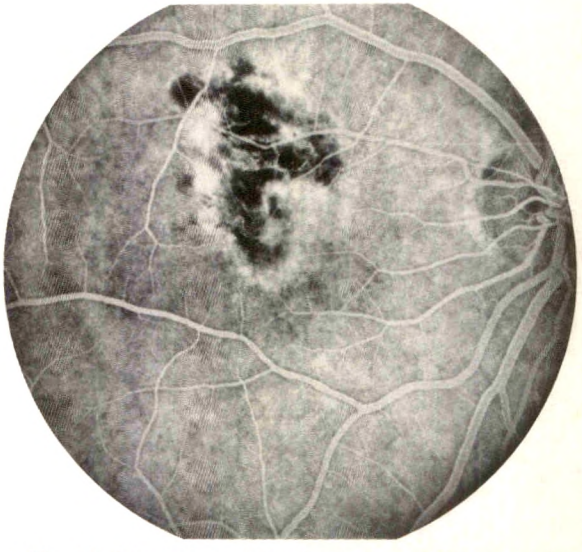


Fig. 10 (Thomas and Kaplan). Case 2. Fluorescein angiogram demonstrating no persistent or recurrent subretinal neovascular membrane postoperatively.

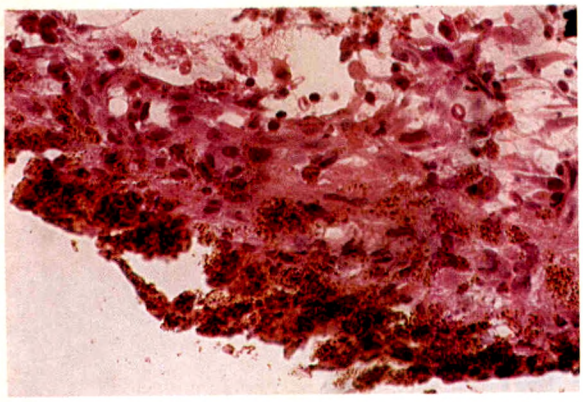


Fig. 11 (Thomas and Kaplan). Case 2. Subfoveal neovascular membrane in which the retinal pigment epithelial cells are at one edge. The basement-membrane matrix contains scattered fibroblasts and endothelial cells (hematoxylin and eosin, × 400).

will have severe visual loss, a small percentage of such patients will maintain good visual acuity. Olk, Burgess, and McCormick[8] identified clinical findings in patients with presumed ocular histoplasmosis that correlated with a good visual outcome: age less than 40 years, good initial visual acuity, membrane extent less than 200 μm beyond the center of the foveal avascular zone, and involvement of less than 50% of the foveal avascular zone. As Campochiaro and associates[9] recently described, some patients with presumed ocular histoplasmosis will have spontaneous involution of the subfoveal neovascular membranes. A pigmented ring around the neovascular membrane may be a favorable prognostic sign. Some cases of improvement in presumed ocular histoplasmosis maculopathy may actually represent resolution of inflammation in a focus of choroiditis, rather than involution of a membrane.

In our two patients, we believe spontaneous improvement or stability was extremely unlikely given the progressive loss of vision, increasing subretinal fluid, enlargement of the membranes, and the occurrence of subretinal hemorrhage in the patient in Case 2.

Argon laser photocoagulation in the Macular Photocoagulation Study[10] was found to be useful in preventing severe visual loss in eyes with extrafoveal subretinal neovascular membranes caused by ocular histoplasmosis. In the observation group, 43 of 90 eyes (48%) lost six or more lines of visual acuity in three years of follow-up, compared with nine of 104 eyes (9%) in the laser treatment group. When the histoplasmic neovascularization was juxtafoveal (1 to 200 μm from the center of the foveal avascular zone), krypton laser was beneficial in preventing severe visual loss.[4] The Macular Photocoagulation Study protocol includes treatment of the entire area of hyperfluorescence on fluorescein angiography in an effort to achieve complete obliteration of the neovascularization. Nevertheless, regardless of the laser treatment modality, there is either direct (thermal) or indirect (by damage to the retinal pigment epithelium) injury of the overlying neurosensory retina. Thus, the preservation of central vision with subfoveal neovascularization after laser treatment is not expected.

The surgical technique we used is a modification of that previously reported for the hemorrhagic and fibrous complications of age-related macular degeneration by de Juan and Machemer,[11] as well as those used for the evacuation of submacular hemorrhage.[12-14] We emphasize the creation of a small retinotomy, followed by the creation of a serous neurosensory detachment. This allows access to the fibrovascular membrane with minimal trauma to the overlying neurosensory retina. We were surprised by the large size of the membranes compared to their fluorescein angiographic appearance, as well as the well-defined character of the fibrovascular proliferation, which appeared to lie on Bruch's membrane and to be intimately associated with the adjacent retinal pigment epithelium. The fibrotic nature of the membranes confirmed by histopathologic examination provided them with a tenacious quality that allowed them to be separated from adjacent normal retinal pigment epithelium and to be grasped by forceps. The fibrovascular membrane appeared to be adherent at the site of the previous photocoagulation scar (Case 1) or to the point at which the subretinal neovascular membrane emanated from the choriocapillaris and extended through Bruch's membrane (Case 2). We speculate that the relatively normal adjacent retinal pigment epithelium filled in the surgical defect by migration, proliferation, or both.

The surgical avulsion of the fibrovascular membrane did not result in significant intraoperative hemorrhage. Intraocular pressure was increased transiently through the infusion cannula at the time of surgical avulsion. However, when intraocular pressure was reduced to normal levels no recurrent bleeding was observed. The area of denuded retinal pigment epithelium and exposed Bruch's membrane was readily

apparent both intraoperatively and postoperatively. We speculate that with the passage of time spreading occurred, as well as proliferation, of adjacent retinal pigment epithelium to cover the defect.

We observed a dramatic improvement in visual acuity (to 20/20 in Case 1 and 20/40+1 in Case 2) in both our patients. The excellent visual recovery in the patient described in Case 1 has now been maintained for 4½ months (seven months since surgery) and in Case 2 for two months (three months since surgery). We remain cautious with regard to the long-term prognosis of this procedure, however, because the underlying pathophysiologic abnormalities have not been reversed. Nevertheless, there has not been a recurrence of subretinal neovascularization postoperatively. Surgical intervention carries its own inherent risks, including retinal tears and detachments, nuclear sclerosis and posterior subcapsular cataract, and microbial endophthalmitis. Only with longer follow-up and additional cases will the relative risks and benefits of such surgery be established.

Recent advances in intraocular surgery have allowed us successfully to remove subfoveal neovascularization associated with the presumed ocular histoplasmosis syndrome through a small retinotomy. Exciting future possibilities include both transposition of retinal pigment epithelium from within the same eye as well as the potential for retinal pigment epithelial and neurosensory transplantation.[15] We have extended our interest in the surgical removal of subfoveal neovascular membranes to age-related macular degeneration and angioid streaks.

References

1. Macular Photocoagulation Study Group: Argon laser for ocular histoplasmosis. Results of a randomized clinical trial. Arch. Ophthalmol. 101:1347, 1983.

2. Macular Photocoagulation Study Group: Krypton laser photocoagulation for neovascular lesions of age-related macular degeneration. Results of a randomized clinical trial. Arch. Ophthalmol. 108:816, 1990.

3. Macular Photocoagulation Study Group: Krypton laser photocoagulation for idiopathic neovascular lesions. Results of a randomized clinical trial. Arch. Ophthalmol. 108:832, 1990.

4. Macular Photocoagulation Study Group: Krypton laser photocoagulation for neovascular lesions of ocular histoplasmosis. Results of a randomized clinical trial. Arch. Ophthalmol. 105:1499, 1987.

5. Woods, A. C., and Wahlen, H. E.: The probable role of benign histoplasmosis in the etiology of granulomatous uveitis. Am. J. Ophthalmol. 49:205, 1960.

6. Schlaegel, T. F., Jr.: Ocular Histoplasmosis. New York, Grune & Stratton, 1977, p.206.

7. Green, W. R.: Retina. In Spencer, W. H. (ed.): Ophthalmic Pathology. An Atlas and Textbook. Philadelphia, W. B. Saunders, 1985, p. 987.

8. Olk, R. J., Burgess, D. B., and McCormick, P. A.: Subfoveal and juxtafoveal subretinal neovascularization in the presumed ocular histoplasmosis syndrome. Ophthalmology 91:1592, 1984.

9. Campochiaro, P. A., Morgan, K. M., Conway, B. P., and Stathos, J.: Spontaneous involution of subfoveal neovascularization. Am. J. Ophthalmol. 109:668, 1990.

10. Macular Photocoagulation Study Group: Argon laser photocoagulation for neovascular maculopathy. Three-year results from randomized clinical trials. Arch. Ophthalmol. 104:694, 1986.

11. de Juan, E., Jr., and Machemer, R.: Vitreous surgery for hemorrhagic and fibrous complications of age-related macular degeneration. Am. J. Ophthalmol. 105:25, 1988.

12. Hanscom, T. A., and Diddie, K. R.: Early surgical drainage of macular subretinal hemorrhage. Arch. Ophthalmol. 105:1722, 1987.

13. Slusher, M. M.: Evacuation of submacular hemorrhage. Technique and timing. Vitreoretinal Surg. Technol. May/June:2, 1989.

14. Wade, E. C., Flynn, H. W., Jr., Olsen, K. R., Blumenkranz, M. S., and Nicholson, D. H.: Subretinal hemorrhage management by pars plana vitrectomy and internal drainage. Arch. Ophthalmol. 108:973, 1990.

15. Silverman, M. S., and Hughes, S. E.: Transplantation of photoreceptors to light-damaged retina. Invest. Ophthalmol. Vis. Sci. 30:1684, 1989.

Causes of Failure After Initial Vitreoretinal Surgery for Severe Proliferative Vitreoretinopathy

Hilel Lewis, M.D., Thomas M. Aaberg, M.D., and Gary W. Abrams, M.D.

We performed initial vitreoretinal surgery on 81 eyes with rhegmatogenous retinal detachments complicated by severe proliferative vitreoretinopathy. Of 81 eyes, 68 (84%) had undergone previous scleral buckling. We performed vitreous base dissection on all 18 eyes (22%) that had anterior proliferative vitreoretinopathy. With one vitreoretinal operation, 66 of 81 eyes (81%) remained totally reattached. The main cause of initial anatomic failure and reoperation was either new or recurrent proliferation at the vitreous base. With additional vitreoretinal surgery and after a mean follow-up period of 19 months, 73 of 81 retinas (90%) were totally reattached. The final causes of anatomic failure were anterior proliferative vitreoretinopathy and proliferation from relaxing retinotomies. Of the 73 successfully reattached eyes, 62 (85%) had postoperative visual acuity of 5/200 or better.

PROLIFERATIVE VITREORETINOPATHY is the most common cause of failure of retinal detachment surgery, which occurs in approximately 7% of all cases.[1,2] The success rates of vitreoretinal surgery in reattaching eyes that develop this complication range from 14% to 80%.[3-22] Lewis and Aaberg[17] emphasized the anterior component to proliferative vitreoretinopathy, defined as cellular proliferation with contraction occurring at or anterior to the posterior insertion of the vitreous base. Based on vector tractional forces, anterior proliferative vitreoretinopathy was classified as anteroposterior, circumferential, and perpendicular. With a broader understanding of all the components and the pathologic anatomy of proliferative vitreoretinopathy and using vitreoretinal surgical techniques that have been derived from this knowledge, we studied the spectrum of results and causes of failure in eyes undergoing vitrectomy for the first time for a rhegmatogenous retinal detachment complicated by severe proliferative vitreoretinopathy.

Accepted for publication Sept. 12, 1990.

From the Jules Stein Eye Institute, Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California (Dr. Lewis); Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia (Dr. Aaberg); and The Eye Institute, Medical College of Wisconsin, Milwaukee, Wisconsin (Dr. Abrams). This study was supported in part by the Charles Kenneth Feldman Fund (Dr. Lewis), and by a nonrestrictive grant to Emory University from Research to Prevent Blindness, Inc.

Reprint requests to Hilel Lewis, M.D., Jules Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90024-7007.

Patients and Methods

Between 1983 and 1986, 81 eyes of 79 patients underwent the first vitreous surgery at the Medical College of Wisconsin for rhegmatogenous retinal detachments complicated by severe proliferative vitreoretinopathy. We included eyes that had undergone previous scleral buckling, but we excluded eyes that had undergone previous vitreous surgery. We also excluded eyes with proliferative vitreoretinopathy secondary to ocular trauma, giant retinal tears, diabetic retinopathy, inflammatory diseases, or vaso-occlusive diseases.

The study group of 81 eyes had a follow-up period ranging from six to 62 months (median, 19 months). At initial manifestation and at the last follow-up examination, we recorded best-corrected visual acuity, anterior and posterior segment examination findings, and intraocular pressure. Posterior proliferative vitreoretinopathy was graded according to the classification adopted by the Retina Society Classification Committee.[23] Anterior proliferative vitreoretinopathy was defined and graded according to the classification proposed by Lewis and Aaberg.[17]

A scleral buckle was placed in the 13 eyes without a pre-existing scleral buckle, and in three eyes the scleral buckle was revised. A

circumferential broad buckling effect was created with a 7-mm grooved silicone tire. A cataractous lens was removed through the pars plana in 12 eyes, and a relatively clear lens was removed in seven eyes to approach anterior proliferative tissue directly. The posterior lens capsule was removed completely by intraocular forceps after breaking the zonules with alpha chymotrypsin.[24] Of the three eyes with an anterior chamber intraocular lens, one eye required an exchange in which the anterior chamber intraocular lens was removed and a posterior chamber intraocular lens was placed. In the remaining two eyes, the anterior chamber intraocular lens was removed but not replaced. A posterior chamber intraocular lens was not removed in the remaining 15 pseudophakic eyes. After the posterior vitreous was removed, scleral depression was used to resect the basal vitreous gel for 360 degrees until no additional vitreous could be removed. In eyes with anterior proliferative tissue, surgical approach to anterior proliferative tissue preceded the release of posterior traction.[17,18] Perpendicular anterior proliferative vitreoretinopathy was released by removing the contracted anterior and posterior hyaloidal surfaces to open the anterior retinal funnel. According to the severity, anteroposterior traction was released by making an incision with the myringotomy blade in the anterior and posterior hyaloidal surfaces or by making an incision with the myringotomy blade and scissors to separate the iris or pars plicata from the posterior insertion of the vitreous base. Once the circumferential retinal trough was opened, the basal vitreous gel was resected with the vitreous cutter until no additional vitreous could be removed and the circumferential retinal trough disappeared.[17,18] Circumferential anterior proliferative vitreoretinopathy was released by incisions transsecting the posterior and anterior borders of the vitreous base until the radial retinal folds that extended posteriorly from the posterior border of the vitreous base were eliminated. Sharp horizontal or vertical cutting scissors were often used in one hand and either an illuminated pick or intraocular forceps (using coaxial light from the operating microscope) in the other hand to fixate the vitreous base while manipulating the scissors through the contracted tissue. After the anterior proliferative tissue was approached, posterior epiretinal membranes were dissected with a combination of a myringotomy blade, illuminated or nonilluminated pick, and intraocular forceps. If subretinal membranes prevented retinal reattachment, they were removed after posterior epiretinal membrane dissection using previously described techniques.[20] Despite anterior and posterior membrane dissection, two eyes had persistent retinal traction that prevented the retina from reattaching, and a relaxing retinotomy was performed. The retina was then reattached by transvitreal evacuation of subretinal fluid together with a fluid-air exchange by an automated air pump. Subretinal fluid was drained through a pre-existing retinal break by a cannulated subretinal fluid aspirator or by performing a drainage retinotomy superior to the optic nerve head. Endolaser photocoagulation was then used to treat all retinal breaks, drainage, or relaxing retinotomies, and was also placed on the scleral buckle indentation at the vitreous base for 360 degrees. In 74 eyes, the air was exchanged with a 14% concentration of perfluoropropane, and in the remaining seven eyes it was replaced with silicone oil. The scleral buckle was elevated before closing the sclerotomies.

Results

Of the 81 patients, 54 were men and 27 were women. The mean age of the patients was 57 years. There were 52 right eyes and 29 left eyes. Forty-nine eyes had undergone previous cataract surgery (18 eyes were pseudophakic), and 68 eyes (84%) had had previous scleral buckling. All 81 eyes had posterior proliferative vitreoretinopathy. According to the Retina Society classification,[23] 19 of 81 eyes (23%) were graded as C1 to C3 proliferative vitreoretinopathy (full-thickness fixed retinal folds in one, two, or three quadrants, respectively) and 62 of 81 eyes (77%) were graded as D1 to D3 proliferative vitreoretinopathy (fixed retinal folds in four quadrants of wide, narrow, or closed funnel shape, respectively). Of 81 eyes, 24 (30%) had a subretinal component to the posterior proliferative vitreoretinopathy. Of 81 eyes, 18 (22%) had anterior proliferative vitreoretinopathy. Of these 18 eyes, 12 (67%) had all three tractional forces, anteroposterior, circumferential, and perpendicular; five eyes (28%) had anteroposterior and circumferential tractional forces; and one eye (6%) had only circumferential anterior proliferative vitreoretinopathy.[17,18]

All 81 eyes were reattached intraoperatively. After the initial vitreoretinal surgery, 29 of the 74 eyes (39%) in which gas was used underwent

an outpatient fluid-gas exchange. After the initial vitreoretinal surgery, 15 of 81 eyes (18.5%) redetached; 13 of these 15 eyes redetached totally and the remaining two eyes redetached only anterior to the scleral buckle. These two eyes had severe hypotony and loss of ocular integrity despite posterior retinal reattachment.

Retinal redetachment occurred three weeks to nine months after surgery, with 13 of the 15 eyes redetaching within four months of surgery. The causes of initial total retinal redetachment included the following: new tissue proliferation at the vitreous base (anterior proliferative vitreoretinopathy) in four of the 15 eyes (27%); recurrent or continued reproliferation at the vitreous base (anterior proliferative vitreoretinopathy) in four eyes (27%); diffuse proliferation of epiretinal tissue in silicone-filled eyes (perisilicone proliferation[25]) in two eyes (13%); reopening of retinal breaks from recurrent posterior epiretinal traction in two eyes (13%); development of a new retinal break from reproliferation of posterior epiretinal tissue in one eye (7%); opening of drainage retinotomy and development of new retinal breaks from reproliferation of posterior subretinal tissue in one eye (7%); and development of an atrophic retinal break in a photocoagulation scar in one eye (7%).

The two eyes that lost ocular integrity despite posterior retinal reattachment had severe hypotony from persistent anterior proliferative vitreoretinopathy, which caused retinal detachment anterior to the scleral buckle that developed as the intraocular gas reabsorbed.

After the initial vitreoretinal surgery, two eyes developed a macular pucker from focal proliferative vitreoretinopathy and underwent additional surgery.

For recurrent retinal detachment, 12 of 81 eyes (15%) underwent two vitreoretinal procedures; two eyes underwent three vitreoretinal procedures (2.5%); and one eye underwent four vitreoretinal procedures (1%).

The indications for the second vitreoretinal operation for a recurrent retinal detachment included anterior proliferative vitreoretinopathy (six eyes), perisilicone proliferation (two eyes), posterior epiretinal proliferative vitreoretinopathy (two eyes), posterior subretinal proliferative vitreoretinopathy (one eye), and new atrophic retinal hole from a photocoagulation scar (one eye). The eye with the new atrophic retinal hole was first treated unsuccessfully with a fluid-gas exchange.

Four patients with anterior proliferative vitreoretinopathy, two patients with total retinal redetachments, and two patients with hypotony and anterior retinal detachments were not reoperated on because of either loss of light perception (one eye) or the patient's unwillingness to undergo additional operations (three eyes).

Of the 12 eyes that underwent a second vitreoretinal operation for a recurrent retinal detachment, four retinas redetached totally (33%), and one additional eye (8%) had a retinal redetachment anterior to the scleral buckle only. The causes of anatomic failure in the four eyes that developed posterior or total retinal redetachment after the second vitreoretinal operation were the development of new anterior proliferative vitreoretinopathy in two eyes and proliferation from relaxing retinotomies in the remaining two eyes.

Of these four eyes, two eyes with new anterior proliferative vitreoretinopathy required a third vitreoretinal procedure. The two eyes that failed because of proliferation from relaxing retinotomies were not reoperated on. Both eyes that underwent a third vitreoretinal surgery were reattached intraoperatively, but neither of them remained attached. The cause of failure in these eyes was proliferation from a relaxing retinotomy. One of these two eyes underwent a fourth vitreoretinal operation, but this eventually failed because of the development of posterior periretinal proliferation. Additional procedures were not performed.

Thus, at the end of the follow-up period, 73 of 81 eyes (90%) were totally reattached, and 76 eyes (94%) were reattached posterior to the scleral buckle. Of the 73 eyes that were totally reattached, 62 (85%) attained final visual acuity of 5/200 or better, with 14 eyes (19%) attaining visual acuity of 20/100 or better. All three eyes with an attached retina posterior to the scleral buckle but a detached anterior retina had final visual acuity of hand motions or worse.

Discussion

Significant advances in the understanding and management of proliferative vitreoretinopathy have occurred.[3-22,26-31] Proliferative vitreoretinopathy is a cell-mediated process characterized by proliferation and contraction of retinal pigment epithelial cells, glial cells, fibrocytes, and macrophages on the periretinal surfaces, vitreous base, and vitreous gel.[26-31]

These cellular membranes exert traction, which, together with retinal breaks, can cause a retinal detachment. To relieve both the tractional and the rhegmatogenous components, vitreous surgery in addition to scleral buckling is required in the management of advanced cases of proliferative vitreoretinopathy.

During the last decade the anatomic success rate of vitreous surgery in the management of proliferative vitreoretinopathy has dramatically increased from 14% to 80%.[3-22] Despite the significant progress, a number of eyes fail after multiple operations with modern vitreoretinal instrumentation, whereas other eyes, despite retinal reattachment, have anterior proliferative vitreoretinopathy with retinal detachment anterior to the scleral buckle and hypotony that can eventually lead to atrophy of the eye.[13,14,17,18,21,22] Vitreoretinal surgeons identify proliferative vitreoretinopathy as the leading problem confronting them.[32]

By emphasizing the anterior component of proliferative vitreoretinopathy, we broadened our understanding of the pathologic anatomy of the disease.[17] The term anterior proliferative vitreoretinopathy is used to define cellular proliferation anterior to the posterior insertion of the vitreous base. Based on the vector tractional forces, anterior proliferative vitreoretinopathy is classified as anteroposterior, circumferential, and perpendicular. Thus, the components of proliferative vitreoretinopathy include an anterior and a posterior component, with proliferative tissue occurring at the vitreous base, epiretinal or subretinal surfaces, and vitreous gel. This improved understanding of the pathologic anatomy as well as of all the components of proliferative vitreoretinopathy has allowed us to develop surgical techniques to manage all components of the disease process.

In a series that included both primary and reoperative procedures, Lewis and Aaberg[17] demonstrated that eyes with an anterior component of proliferative vitreoretinopathy had a worse prognosis when compared to eyes with only a posterior component. Total retinal reattachment was achieved in 59% of eyes with anterior proliferative vitreoretinopathy and increased to 72% in eyes with only a posterior component. Final visual acuity of 5/200 or better was attained in 43% of eyes with anterior proliferative vitreoretinopathy compared to 57% of eyes with only posterior proliferative vitreoretinopathy. The technique used in treating eyes with anterior proliferative vitreoretinopathy was also important in determining the final anatomic and visual prognosis of these eyes. Total retinal reattachment was achieved in 76% of eyes managed with vitreous base surgery and direct approach to anterior membranes, 56% of eyes managed by disconnecting the anterior proliferative tissue from the postequatorial retina by performing relaxing retinotomies, and only 33% of eyes managed with a high and wide scleral buckle and laser demarcation of the anterior proliferative tissue (without vitreous base surgery), in addition to vitrectomy with dissection of posterior periretinal membranes. Moreover, the best visual acuity was attained in those eyes where a direct surgical approach to the anterior membranes was used.[17]

In this series of patients, we attempted to use principles and surgical techniques that would allow us to treat all the components of proliferative vitreoretinopathy. The goal of surgery was to remove all periretinal traction and to close and seal all retinal breaks, while avoiding intraoperative complications and minimizing the risk for postoperative reproliferation.

By using these surgical techniques, we were able with one vitreoretinal procedure to reattach 81% of eyes totally and to reattach 84% of eyes posterior to the scleral buckle. With additional vitreoretinal surgery, the success rate increased to 90% total retinal reattachment and to 94% if we include the three eyes that remained reattached only posterior to the scleral buckle. Additional vitreoretinal surgery was not successful in increasing the success rate, since both eyes that were operated on for a third time eventually redetached.

Similarly, ambulatory vision was attained in a large percentage of cases with 85% of totally reattached eyes attaining final visual acuity of 5/200 or better. The high success rate obtained was achieved by performing one vitreoretinal operation in most patients. Of eyes with intraocular gas, 39% required outpatient fluid-gas exchange. Twelve eyes (15%), two eyes (2%), and one eye (1%) underwent a second, third, and fourth vitreoretinal surgery, respectively, for recurrent retinal detachments. Two additional eyes had repeat vitreoretinal surgery for a macular pucker. This low number of reoperations contrasts to earlier reports where up to 60% of patients with moderate or severe proliferative vitreoretinopathy required reoperations.[19]

The most common cause of anatomic failure was the development of new or recurrent anterior proliferative vitreoretinopathy, which oc-

curred in eight eyes (10%) after the initial vitreoretinal surgery. Other less common causes of failure included posterior epiretinal proliferation with reopening of pre-existing retinal breaks (2%) or creation of new breaks (1%), perisilicone proliferation[25] (2%), subretinal proliferation with reopening of a drainage retinotomy and creation of new retinal breaks (2%), and the development of a retinal hole in an area treated with laser photocoagulation (1%). After the second vitreoretinal operation, an equal number of eyes failed from anterior proliferative vitreoretinopathy and from proliferation along a relaxing retinotomy.

As in the previous study,[17] we found a correlation between the final total retinal reattachment rate and the component of proliferative vitreoretinopathy on initial manifestation. Of the 18 eyes that initially had anterior and posterior proliferative vitreoretinopathy, 16 (89%) remained totally reattached, whereas 61 of the 63 eyes (97%) that initially had only posterior proliferative vitreoretinopathy remained totally reattached. We found no correlation between the rate of retinal reattachment and the initial severity of posterior proliferative vitreoretinopathy.

We believe that a number of factors contribute to our success rate, including the recognition of all the components of proliferative vitreoretinopathy. This recognition allowed us to do the following: approach the vitreous base surgically with direct anterior membrane dissection in all eyes (22%) that initially had anterior proliferative vitreoretinopathy; excise more completely the basal vitreous gel for 360 degrees in all eyes, which significantly reduced the anterior vitreous surface for cells to migrate and proliferate in the postoperative period; completely remove the lens capsule and peripheral lens material; reduce proliferative surfaces and release all periretinal traction; and extend the duration of retinal tamponade in eyes with intraocular gas until adequate chorioretinal adhesions were formed. Another explanation for the results is that, in contrast to other published studies, we excluded eyes that had previously undergone vitreous surgery for persistent or recurrent proliferative vitreoretinopathy. The severity of proliferative vitreoretinopathy in this series, however, was equal if not more severe than that of previously published series.[8,9,13-16,19] Of our 81 patients, 77% showed grade D1 to D3 proliferative vitreoretinopathy (fixed retinal folds in four quadrants of wide, narrow, or closed funnel shape), and 22% had anterior proliferative vitreoretinopathy. Similarly, Hanneken and Michels[19] reported the results of vitreoretinal surgery for proliferative vitreoretinopathy in which 75% of patients had grade D1 to D3 proliferative vitreoretinopathy with an anatomic success rate of 80%.

The three eyes in which the anterior retina detached despite posterior retinal reattachment showed severe chronic hypotony with loss of ocular integrity. Several studies have demonstrated that chronic hypotony is a common cause of functional failure after vitreoretinal surgery for proliferative vitreoretinopathy. We believe that anterior proliferative vitreoretinopathy is the cause of chronic postoperative hypotony in most of these patients. The presumed mechanism of the hypotony is traction exerted by the anterior proliferative tissue on the ciliary body.[18] The anterior proliferative tissue exerts traction on the retina at the vitreous base. If there is no posterior reproliferation or development of new retinal breaks, a high and broad scleral buckle, anterior laser photocoagulation, or both, can limit the detachment anteriorly (occasionally the anterior retinal detachment is minimal and difficult to identify). These eyes, however, frequently develop chronic hypotony and loss of ocular integrity. Therefore, it is preferable to perform surgery at the vitreous base and release the anterior traction directly. This accomplishes anterior retinal reattachment as well as increasing the intraocular pressure. Similarly, in those eyes requiring lensectomy, it is possible that by complete removal of the lens and lens capsule and by more complete excision of the basal vitreous at the time of the first vitreoretinal operation the occurrence of anterior proliferative vitreoretinopathy, hypotony, and recurrent retinal detachment could be decreased.

We have shown that in most eyes with initial proliferative vitreoretinopathy the periretinal traction can be released by membrane dissection. Nonetheless in a few eyes the contractile forces persist despite membrane dissection, and it is in these eyes that a relaxing retinotomy is required to reattach the retina. Fortunately, performing a relaxing retinotomy is rarely required in patients with initial proliferative vitreoretinopathy, as evidenced by only two eyes (2%) that required this procedure in our series. An attempt should be made to avoid relaxing retinotomies if possible because of the high rate of anatomic and visual failure associated with these patients.[21,22]

The goal of surgery in patients with prolifera-

tive vitreoretinopathy should include the release of all anterior and posterior traction. An attempt should also be made to minimize the risk for postoperative reproliferation and redetachment. An important part of our technique is to release the traction at the vitreous base in eyes with anterior proliferative vitreoretinopathy. In eyes without anterior proliferative vitreoretinopathy, it is important to resect the basal vitreous gel until it is flush with either the retina in phakic eyes or the retina and pars plana in aphakic and pseudophakic eyes. By reducing the bulk of basal vitreous there is less vitreous surface for anterior reproliferation.

References

1. The Silicone Study Group: Proliferative vitreoretinopathy. Am. J. Ophthalmol. 99:593, 1985.
2. Rachal, W. F., and Burton, T. C.: Changing concepts of failure after retinal detachment surgery. Arch. Ophthalmol. 97:480, 1970.
3. Schepens, C. L.: Clinical and research aspects of subtotal open-sky vitrectomy. XXXVII Edward Jackson Memorial Lecture. Am. J. Ophthalmol. 91:143, 1981.
4. Gonvers, M.: Temporary silicone oil tamponade in the management of retinal detachment with proliferative vitreoretinopathy. Am. J. Ophthalmol. 100:239, 1985.
5. Lean, J. S., Leaver, P. K., Cooling, R. J., and McLeod, P.: Management of complex retinal detachments by vitrectomy and fluid-silicone exchange. Trans. Ophthalmol. Soc. U.K. 102:203, 1982.
6. Blumenkranz, M. S., Hernandez, E., Ophir, A., and Norton, E. W. D.: 5-Fluorouracil. New applications in complicated retinal detachment for an established antimetabolite. Ophthalmology 91:122, 1984.
7. Parke, D. W., II, and Aaberg, T. M.: Intraocular argon laser photocoagulation in the management of severe proliferative vitreoretinopathy. Am. J. Ophthalmol. 97:434, 1984.
8. Chang, S., Coleman, D. J., Lincoff, H., Wilcox, L. M., Jr., Braunstein, R. A., and Maisel, J. M.: Perfluoropropane gas in the management of proliferative vitreoretinopathy. Am. J. Ophthalmol. 98:180, 1984.
9. de Bustros, S., and Michels, R. G.: Surgical treatment of retinal detachments complicated by proliferative vitreoretinopathy. Am. J. Ophthalmol. 98:694, 1984.
10. Jalkh, A. E., Avila, M. P., Schepens, C. L., Azzolini, C., Duncan, J. E., and Trempe, C. L.: Surgical treatments of proliferative vitreoretinopathy. Arch. Ophthalmol. 102:1135, 1984.
11. Sternberg, P., Jr., and Machemer, R.: Results of conventional vitreous surgery for proliferative vitreoretinopathy. Am. J. Ophthalmol. 100:141, 1985.
12. Ho, P. C., and McMeel, J. W.: Retinal detachment with proliferative vitreoretinopathy. Surgical results with scleral buckling, closed vitrectomy, and intravitreal air injection. Br. J. Ophthalmol. 69:584, 1985.
13. McCuen, B. W., II, Landers, M. B., III, and Machemer, R.: The use of silicone oil following failed vitrectomy for retinal detachment with advanced proliferative vitreoretinopathy. Ophthalmology 92:1029, 1985.
14. Cox, M. S., Trese, M. T., and Murphy, P. L.: Silicone oil for advanced proliferative vitreoretinopathy. Ophthalmology 93:646, 1986.
15. Sell, C. H., McCuen, B. W., II, Landers, M. B., III, and Machemer, R.: Long-term results of successful vitrectomy with silicone oil for advanced proliferative vitreoretinopathy. Am. J. Ophthalmol. 103:24, 1987.
16. Yeo, J. H., Glaser, B. M., and Michels, R. G.: Silicone oil in the treatment of complicated retinal detachment. Ophthalmology 94:1109, 1987.
17. Lewis, H., and Aaberg, T. M.: Anterior proliferative vitreoretinopathy. Am. J. Ophthalmol. 105:277, 1988.
18. Aaberg, T. M.: Management of anterior and posterior proliferative vitreoretinopathy. XLV Edward Jackson Memorial Lecture. Am. J. Ophthalmol. 106:519, 1988.
19. Hanneken, A. M., and Michels, R. G.: Vitrectomy and scleral buckling methods for proliferative vitreoretinopathy. Ophthalmology 95:865, 1988.
20. Lewis, H., Aaberg, T. M., Abrams, G. W., McDonald, R. H., Williams, G. A., and Mieler, W. F.: Subretinal membranes in proliferative vitreoretinopathy. Ophthalmology 96:1403, 1989.
21. Han, D. P., Lewis, M. T., Kuhn, E. M., Abrams, G. W., Mieler, W. F., Williams, G. A., and Aaberg, T. M.: Relaxing retinotomies and retinectomies. Surgical results and predictors of visual outcome. Arch. Ophthalmol. 108:694, 1990.
22. Morse, L. S., McCuen, B. W., II, and Machemer, R.: Relaxing retinotomies. Analysis of anatomic and visual results. Ophthalmology 97:642, 1990.
23. The Retina Society Terminology Committee: The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 90:121, 1983.
24. Lewis, H., Aaberg, T. M., Abrams, G. W., Han, D. P., and Kreiger, A. E.: Management of the lens capsule during pars plana lensectomy. Am. J. Ophthalmol. 103:109, 1987.
25. Lewis, H., Burke, J. M., Abrams, G. W., and Aaberg, T. M.: Perisilicone proliferation after vitrectomy for proliferative vitreoretinopathy. Ophthalmology 95:583, 1988.
26. Machemer, R., and Laqua, H.: Pigment epithelium proliferation in retinal detachment (massive periretinal proliferation). Am. J. Ophthalmol. 80:1, 1975.
27. Laqua, H., and Machemer, R.: Glial cell prolif-

eration in retinal detachment (massive periretinal proliferation). Am. J. Ophthalmol. 80:602, 1975.

28. Van Horn, D. L., Aaberg, T. M., Machemer, R., and Fenzl, R.: Glial cell proliferation in human retinal detachment with massive periretinal proliferation. Am. J. Ophthalmol. 84:383, 1977.

29. Machemer, R., Van Horn, D., and Aaberg, T. M.: Pigment epithelial proliferation in human retinal detachment with massive periretinal proliferation. Am. J. Ophthalmol. 85:181, 1978.

30. Glaser, B. M., Cardin, A., and Biscoe, B.: Proliferative vitreoretinopathy. The mechanism of development of vitreoretinal traction. Ophthalmology 94:327, 1987.

31. Machemer, R.: Proliferative vitreoretinopathy (PVR). A personal account of its pathogenesis and treatment. Invest. Ophthalmol. Vis. Sci. 29:1771, 1988.

32. Report of the National Advisory Eye Council: Vision Research—A National Plan. 1983–1987. Bethesda, Maryland, National Institutes of Health, National Eye Institute, 1982.

OPHTHALMIC MINIATURE

Anwar was right to be concerned about sickness. However, in his childhood, life expectancy in the villages was only thirty-three years. I supervised my children carefully, looking especially at their playmates' eyes to see if they were running or had any discharge at all, symptoms of ophthalmia. For centuries eye disease had been one of Egypt's greatest health problems, and some in the village were blind. Before the clinic came to Mit Abul-Kum, the villagers protected their babies' eyes by lining the lids with kohl, the black powder that Egyptian women had been using for eye makeup since before the days of Cleopatra. Though kohl might have helped, there was still much eye disease all over Egypt from all the dust and the flies which carried the infection from one person to the next.

Jehan Sadat, *A Woman of Egypt*
New York, Pocket Books, 1987, p. 191

Causes of Failure After Repeat Vitreoretinal Surgery for Recurrent Proliferative Vitreoretinopathy

Hilel Lewis, M.D., and Thomas M. Aaberg, M.D.

During the last two years, we performed vitreoretinal surgery on 37 eyes with retinal detachments and recurrent severe proliferative vitreoretinopathy in 37 patients who had had previous failed scleral buckling and vitreous surgery for proliferative vitreoretinopathy. Anterior proliferative vitreoretinopathy was present in 32 of 37 eyes (86%); posterior proliferative vitreoretinopathy of fixed retinal folds in four quadrants of narrow or closed funnel shape occurred in 23 of 37 eyes (62%); and subretinal proliferation was noted in 16 of 37 eyes (43%). The retinas in 12 eyes (32%) redetached from new or recurrent anterior proliferative vitreoretinopathy in nine eyes, reopening of pre-existing retinal breaks in two eyes, or recurrent posterior periretinal proliferation in one eye. With additional vitreoretinal procedures in six eyes and after a mean follow-up period of 11 months, 27 of 37 retinas (73%) were totally reattached, and an additional five eyes (13%) had retinal reattachment posterior to the scleral buckle. Of the 32 patients with posterior retinal reattachment, final visual acuity of 5/200 or better was attained in 19 eyes (59%).

We have initially treated eyes with rhegmatogenous retinal detachments complicated by advanced proliferative vitreoretinopathy by vitreous surgery. Particular attention was given to the removal of the anterior vitreous surface with complete release of anterior and posterior periretinal traction,[1-3] which has resulted in successful total anatomic reattachment in 90% of cases; 85% of these patients have ambulatory vision.[1] Conversely, previous studies of reoperations on eyes with proliferative vitreoretinopathy in which initial vitreous surgery had failed have reported anatomic retinal reattachment posterior to the scleral buckle in only 30% to 65% of cases.[4-7] We performed repeat operations on 37 patients (37 eyes) with recurrent retinal detachments and recurrent proliferative vitreoretinopathy, all of whom had previously undergone unsuccessful vitreous surgery elsewhere.

Patients and Methods

Between January 1988 and December 1989, we operated on 37 eyes of 37 patients with recurrent retinal detachments from recurrent severe proliferative vitreoretinopathy. The operations were performed at the Jules Stein Eye Institute and the Emory Eye Center. We excluded eyes with proliferative vitreoretinopathy that had not been previously operated on with vitreous surgery, as well as eyes with proliferative vitreoretinopathy caused by ocular trauma, giant retinal tears, diabetic retinopathy, inflammatory diseases, or vaso-occlusive diseases.

All eyes had a complete preoperative ophthalmic examination, including testing of best-corrected visual acuity, measurement of intraocular pressure, anterior segment examination, and contact lens and binocular indirect ophthalmoscopy. At each follow-up visit, best-corrected visual acuity testing, measurement of intraocular pressure, anterior and posterior segment examination with biomicroscopy, and indirect ophthalmoscopy were performed.

Echography was performed in eyes with opaque media. Posterior proliferative vitreoretinopathy was graded according to the classification adopted by the Retina Society Classifica-

Accepted for publication Sept. 12, 1990.

From the Jules Stein Eye Institute, Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California (Dr. Lewis); and Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia (Dr. Aaberg). This study was supported in part by the Charles Kenneth Feldman Fund (Dr. Lewis), and by a nonrestrictive grant to Emory University from Research to Prevent Blindness, Inc. This study was presented at the XVIIth Meeting of the Club Jules Gonin, Lausanne, Switzerland, Sept. 4, 1990.

Reprint requests to Hilel Lewis, M.D., Jules Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90024-7007.

tion Committee.[8] Anterior proliferative vitreoretinopathy was defined and graded according to the classification proposed by us.[2]

The surgical techniques we used have been previously described.[1-3,9-11] A scleral buckle was revised in two eyes. The crystalline lens was removed through the pars plana in four of five phakic eyes (80%). One of these four lenses was minimally opacified but was removed to be able to approach the anterior proliferative tissue surgically. Of the 17 eyes with an intraocular lens, a posterior chamber intraocular lens was present in 15 eyes and removed in two eyes. Both eyes with an anterior chamber intraocular lens had the lenses removed at the time of vitreoretinal surgery. In all 37 eyes, residual anterior vitreous was resected for 360 degrees while scleral depression was performed. A direct bimanual surgical approach was used in all 32 eyes with anterior proliferative vitreoretinopathy. The posterior epiretinal membranes were dissected in all 37 cases. In seven of the 16 eyes (44%) with subretinal proliferation, the subretinal membranes were surgically cut or removed because they were exerting traction that prevented retinal reattachment. Despite anterior and posterior membrane dissection, three eyes had persistent retinal traction that prevented the retina from reattaching, and a relaxing retinotomy was performed. Intraocular gas (perfluoropropane) was used in 29 eyes (78%) and silicone oil (1,000 centistokes) was used in eight eyes (22%). In seven of these eight eyes, silicone oil was used because the patients had to use air travel. Endophotocoagulation was used in all eyes to treat all retinal breaks, drainage, or relaxing retinotomies, and was also placed on the scleral buckle indentation at the vitreous base for 360 degrees.

Results

Of the 37 patients included in this study, 25 were male and 12 were female. There were 14 right eyes and 23 left eyes. The mean age of the patients was 55 years (range, 12 to 76 years). The follow-up period ranged from six months to 24 months (median, 11 months). All 37 eyes had scleral buckling for rhegmatogenous retinal detachments before initial vitrectomy. The mean number of previous vitreoretinal operations for proliferative vitreoretinopathy was 1.43 per eye. Of 37 eyes, 15 (40.5%) were preoperatively aphakic, 17 (46%) were pseudophakic, and five (13.5%) were phakic.

All 37 eyes had posterior proliferative vitreoretinopathy. Seven eyes (19%) had grade C3 (full-thickness retinal folds in three quadrants); eight eyes (22%) had grade D1 (fixed retinal folds in four quadrants of wide funnel shape); 13 eyes (35%) had grade D2 (fixed retinal folds in four quadrants of narrow funnel shape); and nine eyes (24%) had grade D3 (fixed retinal folds in four quadrants of closed funnel shape) posterior proliferative vitreoretinopathy. Of 37 eyes, 16 (43%) had subretinal proliferation. Anterior proliferative vitreoretinopathy was noted in 32 of 37 eyes (86%). Of these 32 eyes, 17 (53%) had anteroposterior and circumferential tractional forces, and 15 eyes (47%) had only anteroposterior tractional forces.

The retina was successfully reattached intraoperatively in all 37 eyes. A postoperative fluid-gas exchange was performed in six of the 29 eyes (21%) in which gas was used. Iridocorneal adhesion requiring reformation of the anterior chamber with sodium hyaluronic acid developed in one patient. In three eyes, tissue plasminogen activator was injected intraocularly because of the development of severe postvitrectomy fibrin response. Silicone oil was removed two to three months after injection in three of the eight eyes (37%) in which it was used. Two eyes in which silicone oil was used required penetrating keratoplasty because of corneal decompensation.

During the follow-up period, 12 of the 37 eyes (32%) redetached. In all 12 eyes, the retinal redetachment was total. The retinal redetachment occurred one week to three months after surgery. In these 12 eyes, the causes for retinal redetachment included the following: new anterior proliferative vitreoretinopathy with reopening or development of new retinal breaks in five eyes (14%) (three of the five eyes with silicone oil); recurrent proliferation at the vitreous bases (anterior proliferative vitreoretinopathy) in four eyes (11%) (three of the four eyes with silicone oil); reopening of retinal breaks because of lack of chorioretinal adhesion in two eyes (5%); and posterior periretinal proliferation in one eye (3%).

All 12 patients with retinal redetachments were offered additional surgery, but three patients declined (all three with silicone oil). Of the nine eyes that were reoperated on, vitreoretinal surgery was performed in seven eyes and an outpatient fluid-gas exchange followed by laser photocoagulation was performed in two eyes (both had redetachment of the retina from reopening of retinal breaks without periretinal traction). Of the seven eyes reoperated

on with vitreoretinal surgery, we performed two operations in three eyes, three operations in three eyes, and four operations in one eye. The indications for the second reoperation were new anterior proliferative vitreoretinopathy in three eyes, recurrent anterior and posterior proliferative vitreoretinopathy in two eyes, perisilicone proliferation in one eye, and an exaggerated macular pucker in one eye. The indications for the third and fourth reoperations were recurrent anterior and posterior proliferative vitreoretinopathy in all cases.

At the last follow-up examination, 27 of the 37 eyes (73%) were totally reattached, and 32 eyes (86%) were reattached posterior to the scleral buckle. The causes of final total retinal detachment included anterior and posterior perisilicone proliferation in three eyes (8%), and recurrent anterior proliferative vitreoretinopathy in two eyes (5%). In the five eyes with final retinal detachment anterior to scleral buckle only, new or recurrent anterior proliferative vitreoretinopathy was the cause of failure in all eyes (three with silicone oil).

Intraocular pressure at the last follow-up visit ranged from 2 to 20 mm Hg (mean, 13 mm Hg). Of 37 eyes, 24 had increased intraocular pressure when compared to preoperative levels. An intraocular pressure of less than 5 mm Hg was noted in three of the five eyes with total retinal detachment, and in four of the five eyes with anterior retinal detachment but posterior retinal reattachment. Four of the eight eyes in which silicone oil was used had final intraocular pressure of less than 5 mm Hg when compared to six of the 29 eyes (21%) in which gas was used.

Of the 27 eyes that were totally reattached, 18 (67%) attained final visual acuity of 5/200 or better, with three eyes (11%) attaining visual acuity of 20/100 or better. Four of the five eyes with an attached retina posterior to the scleral buckle but a detached anterior retina had final visual acuity of light perception.

Discussion

Of 37 consecutive eyes in which vitreoretinal surgery for retinal detachments with proliferative vitreoretinopathy had previously failed, we achieved total retinal reattachment in 27 eyes, retinal reattachment posterior to the scleral buckle in 32 eyes, and ambulatory vision in 19 eyes by removing the anterior vitreous surface, completely releasing the anterior and posterior periretinal traction, and using intraocular tamponade and endophotocoagulation.

These results in recurrent proliferative vitreoretinopathy are lower than those in eyes with advanced proliferative vitreoretinopathy operated on for the first time by us using similar vitreoretinal surgical techniques. In that series, 66 of 81 eyes (81%) were totally reattached with one operation, and 73 of 81 eyes (90%) were totally reattached with two operations (reattachment posterior to the scleral buckle in 76 of 81 eyes [94%]).[1]

We believe that the lower success rate achieved in patients reoperated on for recurrent proliferative vitreoretinopathy can be explained by the much higher prevalence of anterior proliferative vitreoretinopathy in these eyes when compared to eyes with initial proliferative vitreoretinopathy. Eyes with advanced proliferative vitreoretinopathy but without previous vitreous surgery had a 22% prevalence of anterior proliferative vitreoretinopathy,[1] whereas 86% of eyes that had failed vitreous surgery had anterior proliferative vitreoretinopathy. In contrast, the severity of posterior proliferative vitreoretinopathy and the prevalence of subretinal proliferation was similar in both groups of patients. These observations support our previous findings that eyes with anterior proliferative vitreoretinopathy have a worse prognosis than eyes with only posterior proliferative vitreoretinopathy.[1-3]

Adequate initial surgical management of eyes with retinal detachment and severe proliferative vitreoretinopathy carries the best chances for anatomic success. The goal of surgery in proliferative vitreoretinopathy should be to achieve stable total retinal reattachment, while minimizing the risks of complications and reproliferation. New or recurrent anterior proliferative vitreoretinopathy is the most common cause of failure after vitreoretinal surgery for retinal detachment with proliferative vitreoretinopathy.[1] We believe that by initially removing as much as possible of the basal vitreous gel (Figs. 1 and 2) and completely removing the lens or lens remnants, the risk of developing postoperative anterior proliferative vitreoretinopathy is decreased. Similarly, initial adequate management of the anterior component of proliferative vitreoretinopathy with complete release of traction increases the chances for achieving total retinal reattachment and decreases the likelihood of developing hypotony with atrophy of the eye despite posterior retinal reattachment.

It has been suggested that silicone oil tam-

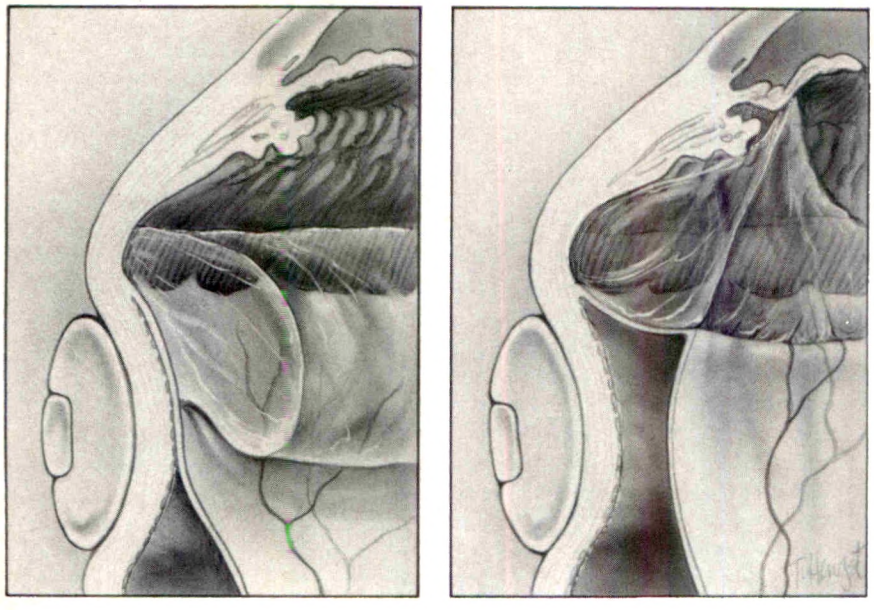


Fig. 1 (Lewis and Aaberg). Left, Residual basal vitreous gel after posterior vitrectomy. Right, Anterior vitreous gel becomes adherent to the pars plana, pars plicata, and posterior surface of the iris causing anterior displacement of the posterior border of the vitreous base with an anterior retinal detachment and hypotony.

ponade should be considered in eyes with recurrent proliferative vitreoretinopathy that have failed conventional vitreoretinal surgical techniques.[5-6] It is our impression that successful results in these complicated cases are primarily caused by the complete intraoperative release of anterior and posterior periretinal traction, removal of the basal vitreous gel and lens remnants, and use of intraoperative or postoperative photocoagulation rather than the intraocular tamponade. In our series, 29 of 37 eyes (76%) were treated with intraocular gas. The indication for silicone oil in seven of the eight eyes in which it was used was the need of the patient to travel by air soon after the operation. Although the severity of the disease was not greater in the eyes in which silicone oil was used, the complications and redetachment rate were greater when compared to the eyes in which intraocular tamponade with gas was used.

If the anterior and posterior periretinal trac-

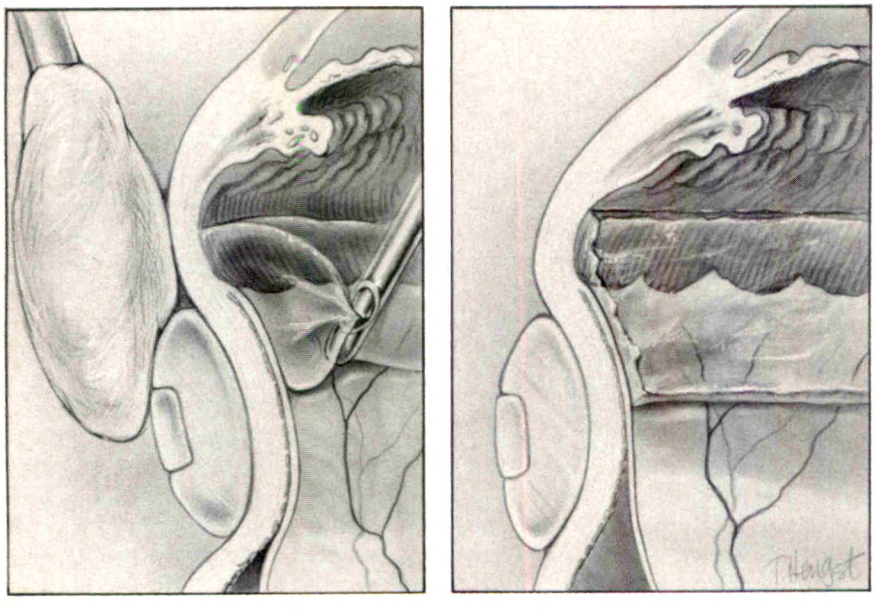


Fig. 2 (Lewis and Aaberg). Left, Removal of anterior vitreous gel by indenting the sclera in the region of the vitreous base. Right, Excising the basal vitreous gel reduces the anterior vitreous surface and decreases the chances of developing anterior proliferative vitreoretinopathy.

tion can be completely released intraoperatively, a long-acting or permanent tamponade such as silicone oil is probably not required. Photocoagulation scars form a chorioretinal adhesion within weeks, and therefore intraocular gas is sufficient to maintain retinal tamponade until the chorioretinal adhesion forms. If retinal traction is not relieved, the only advantage of silicone oil when compared to gas is that it may localize the retinal detachment for some time. If the traction is not eventually relieved, however, the eye may become hypotonous or the detachment can extend.

The release of anterior traction can increase intraocular pressure and prevent atrophia bulbi in some eyes. Despite total retinal reattachment and lack of anterior traction, however, four of 37 of eyes (11%) remained hypotonous (intraocular pressure less than 5 mm Hg) at the last follow-up visit. This hypotony in the absence of ciliary body traction could possibly be explained by either the inability of the cells to produce or secrete aqueous humor because of damage from chronic traction, or because of damage to the ciliary body from multiple operations.

Despite significant advances in the surgical management of proliferative vitreoretinopathy, the basic disease process may continue and lead to surgical failure. Further developments in the prevention of factors that promote the development of this disease, together with pharmacologic treatment, will lead to a greater success rate and improved visual function in such patients.

References

1. Lewis, H., Aaberg, T. M., and Abrams, G. W.: Causes of failure after initial vitreoretinal surgery for severe proliferative vitreoretinopathy. Am. J. Ophthalmol. 111:8, 1991.

2. Lewis, H., and Aaberg, T. M.: Anterior proliferative vitreoretinopathy. Am. J. Ophthalmol. 105:277, 1988.

3. Aaberg, T. M.: Management of anterior and posterior proliferative vitreoretinopathy. XLV Edward Jackson Memorial Lecture. Am. J. Ophthalmol. 106:519, 1988.

4. Diddie, K. R., Stern, W. H., Ober, R. R., Irvine, A., and Ryan, S. J.: Intraocular silicone oil for recurrent proliferative vitreoretinopathy in vitrectomized eyes. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1983, p. 173.

5. McCuen, B. W., II, Landers, M. B., III, and Machemer, R.: The use of silicone oil following failed vitrectomy for retinal detachment with advanced proliferative vitreoretinopathy. Ophthalmology 92:1029, 1985.

6. Cox, M. S., Trese, M. T., and Murphy, P. L.: Silicone oil for advanced proliferative vitreoretinopathy. Ophthalmology 93:646, 1986.

7. Sell, C. H., McCuen, B. W., II, Landers, M. B., III, and Machemer, R.: Long-term results of successful vitrectomy with silicone oil for advanced proliferative vitreoretinopathy. Am. J. Ophthalmol. 103:24, 1987.

8. The Retina Society Terminology Committee: The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 90:121, 1983.

9. Lewis, H., Aaberg, T. M., Abrams, G. W., McDonald, R. H., Williams, G. A., and Mieler, W. F.: Subretinal membranes in proliferative vitreoretinopathy. Ophthalmology 96:1403, 1989.

10. Han, D. P., Lewis, M. T., Kuhn, E. M., Abrams, G. W., Mieler, W. F., Williams, G. A., and Aaberg, T. M.: Relaxing retinotomies and retinectomies. Surgical results and predictors of visual outcome. Arch. Ophthalmol. 108:694, 1990.

11. Lewis, H., Aaberg, T. M., Abrams, G. W., Han, D. P., and Kreiger, A. E.: Management of the lens capsule during pars plana lensectomy. Am. J. Ophthalmol. 103:109, 1987.

Prevalence of Lattice Degeneration and Its Relation to Axial Length in Severe Myopia

José M. Celorio, M.D., and Ronald C. Pruett, M.D.

We studied 436 eyes of 218 patients with myopia of -6.00 diopters or more in both eyes. Of 218 patients, 72 (33.0%) had lattice degeneration of the retina. Among these 72 patients, lattice lesions were uniocular in 39 (54.2%) and binocular in 33 (45.8%). Of 105 males, 33 (31.4%) had lattice degeneration; of 113 females, 39 (34.5%) had lattice degeneration. Contrary to previously published data, we found an inverse relationship between axial length and the prevalence of lattice degeneration in severely myopic eyes. The greatest prevalence of lattice degeneration (63 of 154 eyes, 40.9%) was found in eyes with an axial length of 26.0 to 26.9 mm (−6.00 to −8.70 diopters), and the least prevalence of lattice degeneration (five of 71 eyes, 7.0%) was found in eyes with an axial length of 32.0 mm (−24.00 diopters) or greater. This may explain the observation that retinal detachment after cataract surgery has been noted more commonly among patients with moderate than severe myopia.

LATTICE DEGENERATION of the retina has been described in numerous reports since the turn of the century.[1-4] Typical lesions are sharply defined, circumferentially oriented areas of retinal thinning located anterior to the fundus equator.[5] A fishbone or crosshatch pattern of sclerotic, white retinal arterioles and venules within the base of a lesion is a frequent finding.[6] The vitreous gel shows liquefaction over a lattice lesion and a condensed adhesion along its margin. Lattice degeneration is recognized as a frequent cause of retinal detachment because of small round holes that occur within the areas of degeneration and tractional tears along the edge of the defects.[3-11] Lattice degeneration also is found in asymptomatic eyes; its prevalence has been variously reported as 4.5%,[12] 6.0%,[13] 7.1%,[14] and 9.5%.[15] Straatsma and associates[5] found lesions in 10.7% of autopsy eyes.

Lattice degeneration occurs more frequently among myopic than nonmyopic eyes and contributes to the tendency of retinal detachment to develop in myopic eyes.[16-19] In the study by Karlin and Curtin[20] of 1,437 eyes, the prevalence of lattice degeneration was correlated with axial length. Although we have believed this to be true, we were not finding lattice degeneration as frequently as expected in our patients with extreme degrees of myopia. We conducted a study to reexamine this association, specifically among those patients with myopia of −6.00 diopters or more.

Patients and Methods

Computer-derived records on patients coded as having myopia of −6.00 diopters or greater in both eyes were reviewed without regard to the initial symptoms or findings, including retinal detachment. Excluded from the study were patients with myopia associated with retinopathy of prematurity and those with incomplete documentation of bilateral fundus findings because of opaque media, poorly dilating pupils, or surgical anophthalmos. The records of 436 eyes of 218 patients, including 105 males and 113 females, ranging in age from 10 to 72 years, were included in the study. Most patients had been examined on numerous occasions over a number of years, thus decreasing the chance that lattice lesions might be undetected. Available data included visual acuity and ocular tension measurements, refractions, stereoscopic color photographs, and, in many cases, fluo-

Accepted for publication Oct. 12, 1990.

From Retina Associates, Eye Research Institute, and Harvard Medical School, Boston, Massachusetts. This study was supported in part by the Myopia Research Fund of the Eye Research Institute.

Reprint requests to Ronald C. Pruett, M.D., Eye Research Institute, 20 Staniford St., Boston, MA 02114.

P 24 327

rescein angiograms. All eyes were evaluated by indirect ophthalmoscopy with 360-degree scleral depression and by biomicroscopy with a three-mirror Goldmann contact lens. The criteria for lattice degeneration were those classically described and illustrated in published reports.[4-6] Standardized immersion A-scan axial length measurements and usually B-scan ultrasonic studies were done.

Eyes were classified into seven groups on the basis of axial length. The shortest axial diameter was 26.0 mm (−6.00 diopters), and the longest was 32.0 mm (−24.00 diopters) or greater, up to 40.0 mm (−48.00 diopters) (Table).

Results

Of the 436 eyes of 218 patients, 105 eyes (24.1%) of 72 patients (33.0%) showed lattice retinal degeneration. The patients with lattice degeneration included 33 of 105 males (31.4%) and 39 of 113 females (34.5%). Of the 72 patients with lattice degeneration, 33 (45.8%) were male and 39 (54.2%) were female. Lattice degeneration occurred uniocularly in 39 patients (54.2%) and binocularly in 33 patients (45.8%). The lesions were located most often in the temporal quadrants (94 of 105 eyes, 89.5%). Of the 105 eyes with lattice degeneration, 36 (34.3%) had a single lesion, and 69 (65.7%) had two or more lesions. Young adults aged 21 to 40 years were most frequently affected by lattice degeneration (51 of 160 eyes, 31.9%), and patients older than 60 years of age were least affected (11 of 68 eyes, 16.2%). Among those aged 20 years or younger, 16 of 78 eyes (20.5%) had lattice degeneration, and among those 41 to 60 years of age, 27 of 130 eyes (20.8%) had lattice degeneration. The highest prevalence of lattice degeneration (63 of 154 eyes, 40.9%) was found among eyes of axial length 26.0 to 26.9 mm; the lowest prevalence of lattice degeneration (five of 71 eyes, 7.0%) was found among eyes of axial length 32.0 mm or greater (Fig. 1).

TABLE
CHARACTERISTICS OF STUDY POPULATION

AXIAL LENGTH (MM)	NO. OF EYES	SEX		AGE (YRS)	
		MALE	FEMALE	RANGE	MEAN
26.0–26.9	154	75	79	7–62	34.5
27.0–27.9	84	40	44	8–70	39.0
28.0–28.9	24	10	14	15–64	39.5
29.0–29.9	35	17	18	10–55	32.5
30.0–30.9	32	16	16	12–58	35.0
31.0–31.9	36	18	18	16–65	40.5
32.0–40.0	71	34	37	7–66	36.5
Total	436	210	226	7–70	36.7

Discussion

In many respects our statistics are congruent with those reported by others. Lattice degeneration was only slightly more common among females. Our finding of 45.8% (33 of 72 eyes) bilaterally affected was similar to the data of Shiomi[15] (31.6%), Byer[14] (34%), and Karlin and Curtin[20] (40%), but differed from the results of Morse[21] (66.5%) who studied only patients with retinal detachment. Age did not appear to have a major influence on prevalence, but lattice degeneration was less frequently found in our older patients, as documented previously.[5,14,15,20] We have no explanation for this finding, although one might speculate that lattice degeneration could be more difficult to detect in older eyes with lens opacities and peripheral pigmented fundus changes.

Overall we found lattice degeneration in 105 of 436 eyes (24.1%) with −6.00 diopters or more of myopia, which is in close agreement with the findings of Cambiaggi, Sanna, and Nervi[12] (20%). Kirker and McDonald,[22] studied 101 eyes of 54 patients with myopia of −6.00 diopters or greater and found that only 3% had lattice degeneration. They commented that this figure seemed low. We would agree, especially in view of the 6% prevalence of lattice degeneration found by Rutnin and Schepens[23,24] in normal eyes and the 10.7% prevalence in autopsy eyes.[5] Kirker and McDonald[22] offered possible explanations for this discrepancy: different populations, different examination methods, or variations in the examiners' definitions. Different examination methods and variations in the examiners' definitions probably played a role. Data for their study were derived from indirect ophthalmoscopy but without scleral depression, and the examinations were performed by ophthalmology residents in training.

Although we were pleased that our statistical findings in the patients with severe myopia confirmed our informal clinical observations, we faced the problem of explaining the inverse relationship between lattice degeneration and

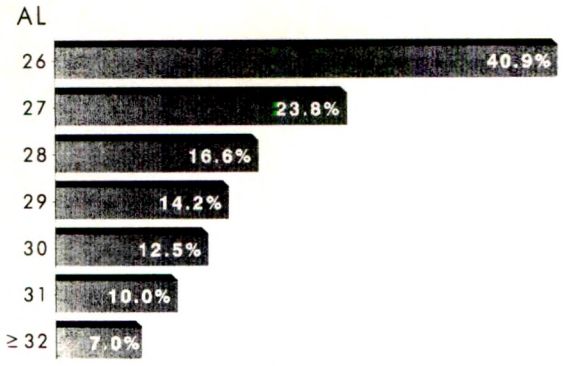


Fig. 1 (Celorio and Pruett). Prevalence of lattice degeneration in 436 eyes according to axial length (AL; mm).

axial length. Shiomi[15] reported on lattice degeneration in Japanese patients. Among 518 eyes with myopia of −8.00 diopters or less, 39 (7.5%) had lattice degeneration, whereas among 29 eyes with myopia of −8.25 to −22.00 diopters, only one (3.4%) had lattice degeneration. Most often affected were eyes with moderate myopia between −2.25 and −8.00 diopters (17 of 111 eyes, 15.3%). Although this relationship was not the emphasis of his report, Shiomi's observations also suggested that lattice degeneration is less frequent in eyes with severe myopia, despite the genetic differences between his patient population and our own.

Karlin and Curtin[20] indicated that lattice degeneration was present in 11% of eyes with an axial length of 26.5 mm (−7.50 diopters) or more (Fig. 2). Their series and ours were drawn from mixed populations of the Northeast, and both were examined by experienced observers who probably agreed closely on diagnostic criteria. The most important difference, we believe, is the manner in which patients were selected for examination. The source of the patients in the Karlin and Curtin study was a myopia clinic. Perhaps more patients came on their own for examination rather than being referred for a specific problem. Most of our patients were referred for examination by other ophthalmologists. The reasons for referral varied widely: a routine examination for myopia, family history of a retinal disorder, symptoms of photopsia and floaters, glaucoma, fundus examination before or after cataract surgery, and treatment of macular degeneration or retinal detachment, among others. Although none of these categories was excluded from our study, the mix of patients may have differed from that of Karlin and Curtin.[20] Obviously the composition of both study groups was influenced by multiple factors, including racial and socioeconomic aspects of the referral base, and these remain unknown in both series. Only an unselected population survey could attempt to measure accurately the true prevalence of lattice degeneration among patients with myopia of various degrees.

Further studies of the relationship between axial length and lattice degeneration would be useful. An inverse relationship might explain why patients with moderate myopia have been more prone than patients with severe myopia to retinal detachment after cataract surgery. Smith and associates[25] reported statistics that describe this complication after 3,065 consecutive extracapsular cataract extractions with posterior chamber intraocular lens implantation. The incidence of retinal detachment for the moderately myopic group (axial length greater than 25.0 and less than 26.5 mm, −3.00 to −7.50 diopters) was 6.3%; and for the severely myopic group (axial length greater than 26.5 mm, greater than −7.50 diopters), the incidence was 4.8%. Lattice degeneration was the most common predisposing retinal lesion; it

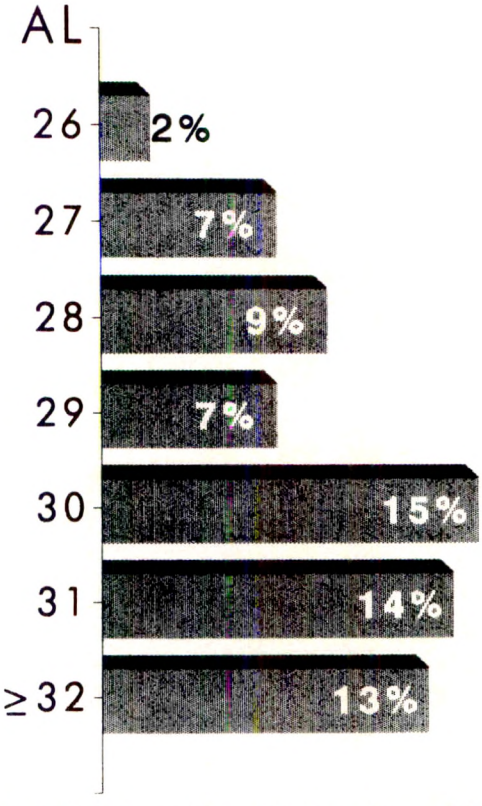


Fig. 2 (Celorio and Pruett). Prevalence of lattice degeneration according to axial length (AL; mm) as reported by Karlin and Curtin.[20]

was found in 13.6% of the eyes with retinal detachment and only 2.0% of age-matched control eyes. The authors remarked on the low degree of axial myopia (mean axial length, 25.09 mm, −3.27 diopters) that correlated with retinal detachment.[25]

An inverse relationship between lattice degeneration and axial length could also support the belief that progressive myopia is a condition distinct from the more common mild degrees of myopia. The response to topical corticosteroids suggests such a difference. During corticosteroid instillation in severely myopic eyes, intraocular tension usually increases, which is similar to that seen in relatives of patients with open-angle glaucoma.[26-30] This response is not usually observed in patients with mild myopia. Lattice degeneration may be more closely linked genetically with mild (physiologic) than with severe (pathologic) myopia.

References

1. Gonin, J.: La pathogénie du décolle spontané de la rétine. Ann. Ocul. 132:30, 1904.
2. Vogt, A.: Die operative Therapie und die Pathogenese der Netzhautablosung. Stuttgart, Enke, 1936.
3. Schepens, C. L.: Subclinical retinal detachments. Arch. Ophthalmol. 47:593, 1952.
4. Straatsma, B. R., and Allen, R. A.: Lattice degeneration of the retina. Trans. Am. Acad. Ophthalmol. Otolaryngol. 66:600, 1962.
5. Straatsma, B. R., Zeegen, P. D., Foos, R. Y., Feman, S. S., and Shabo, A. L.: Lattice degeneration of the retina. XXX Edward Jackson Memorial Lecture. Am. J. Ophthalmol. 77:619, 1974.
6. Schepens, C. L.: Retinal Detachment and Allied Diseases, vol. 1. Philadelphia, W. B. Saunders, 1983, pp. 154–156.
7. Dumas, J., and Schepens, C. L.: Chorioretinal lesions predisposing to retinal breaks. Am. J. Ophthalmol. 61:620, 1966.
8. Michaelson, I. C.: Role of a distinctive choroido-retinal lesion in the pathogenesis of retinal hole. A clinical and pathological report. Br. J. Ophthalmol. 40:527, 1956.
9. Byer, N. E.: Lattice degeneration of the retina. Surv. Ophthalmol. 23:213, 1979.
10. Laatikainen, L.: The fellow eye in patients with unilateral retinal detachment. Findings and prophylactic treatment. Acta Ophthalmol. 63:546, 1985.
11. Folk, J. C., Arrindell, E. L., and Klugman, M. R.: The fellow eye of patients with phakic lattice retinal detachment. Ophthalmology 96:72, 1989.
12. Cambiaggi, A., Sanna, G., and Nervi, I.: Contributo alla conoscenza della degenerazione a graticciata della retina. Suoi rapporti con la miopia ed il distacco retinico. Ann. Oftalmol. 91:314, 1965.
13. Halpern, J. I.: Routine screening of the retinal periphery. Am. J. Ophthalmol. 62:99, 1966.
14. Byer, N. E.: Clinical study of lattice degeneration of the retina. Trans. Am. Acad. Ophthalmol. Otolaryngol. 69:1064, 1965.
15. Shiomi, Y.: Study of lattice degeneration of the retina. Part 2. Clinical features of lattice degeneration of the retina. Acta Soc. Ophthalmol. Jpn. 85:269, 1981.
16. Byer, N. E.: Changes in and prognosis of lattice degeneration of the retina. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78:OP114, 1974.
17. Murakami-Nagasako, F., and Ohba, N.: Phakic retinal detachment associated with atrophic hole of lattice degeneration of the retina. Graefes Arch. Clin. Exp. Ophthalmol. 220:174, 1983.
18. Hyams, S. W., and Neumann, E.: Peripheral retina in myopia with particular reference to retinal breaks. Br. J. Ophthalmol. 53:300, 1969.
19. Burton, T. C.: The influence of refractive error and lattice degeneration on the incidence of retinal detachment. Trans. Am. Ophthalmol. Soc. 87:143, 1989.
20. Karlin, D. B., and Curtin, B. J.: Peripheral chorioretinal lesions and axial length of the myopic eye. Am. J. Ophthalmol. 81:625, 1976.
21. Morse, P. H.: Lattice degeneration of the retina and retinal detachment. Am. J. Ophthalmol. 78:930, 1974.
22. Kirker, G. E. M., and McDonald, D. J.: Peripheral retinal degeneration in high myopia. Can. J. Ophthalmol. 6:58, 1971.
23. Rutnin, U., and Schepens, C. L.: Fundus appearance in normal eyes. III. Peripheral degenerations. Am. J. Ophthalmol. 64:1040, 1967.
24. ———: Fundus appearance in normal eyes. IV. Retinal breaks and other findings. Am. J. Ophthalmol. 64:1063, 1967.
25. Smith, P. W., Stark, W. J., Maumenee, A. E., Enger, C. L., Michels, R. G., Glaser, B. M., and Bonham, R. D.: Retinal detachment after extracapsular cataract extraction with posterior chamber intraocular lens. Ophthalmology 94:495, 1987.
26. Podos, S. M., Becker, B., and Morton, W. R.: High myopia and primary open-angle glaucoma. Am. J. Ophthalmol. 62:1039, 1966.
27. Amba, S. K., Jain, I. S., and Gupta, S. D.: Topical corticosteroids and intra-ocular pressure in high myopia. I. Study of pressure response. Indian J. Ophthalmol. 21:102, 1973.
28. Jain, I. S., Amba, S. K., and Gupta, S. D.: Topical corticosteroids and intra-ocular pressure in high myopia. II. Relationship of pressure response to age, dioptric power, degenerative changes in the eye, and scleral rigidity. Indian J. Ophthalmol. 21:108, 1973.
29. Wang, R., and Guo, B.: Steroid-induced ocular hypertension in high myopia. Chin. Med. J. 97:24, 1984.
30. Thomas, J. V., and Pruett, R. C.: Steroid provocation testing in high myopia. Proceeding of the Third International Conference on Myopia, May 1986, Rome, p. 375.

Ocular Clinicopathologic Study of Gyrate Atrophy

David J. Wilson, M.D., Richard G. Weleber, M.D., and W. Richard Green, M.D.

We performed a histopathologic study of whole globes obtained post mortem from a patient with well-documented, vitamin B6–responsive gyrate atrophy. The retina in the posterior pole had focal areas of photoreceptor atrophy with adjacent retinal pigment epithelial hyperplasia. An abrupt transition from the near normal retina to a zone of near total atrophy of the retina, retinal pigment epithelium, and choroid was present in the fundus midperiphery. Electron microscopic examination disclosed abnormalities of the mitochondria of the corneal endothelium and the nonpigmented ciliary epithelium. Similar, but less severe, mitochondrial abnormalities were present in the photoreceptors.

GYRATE ATROPHY is a rare autosomal recessive disease caused by a deficiency of the mitochondrial matrix enzyme ornithine-delta-aminotransferase. This pyridoxal phosphate-dependent enzyme converts alpha-ketoglutarate and ornithine to glutamate and glutamate-gamma-semialdehyde, which through delta[1]-pyrroline-5-carboxylate is involved in the synthesis of proline. The ocular manifestations of this progressive disorder have been reviewed[1] and include a characteristic retinochoroidal atrophy (Fig. 1), cataracts, myopia, blunting of the ciliary processes, and iris atrophy. Two clinical subtypes of gyrate atrophy have been defined, based on in vivo or in vitro evidence of response to vitamin B6, which is the cofactor of the enzyme ornithine aminotransferase. Vitamin B6 responsiveness is manifested in vivo by an approximate 50% reduction in serum ornithine levels and normalization of serum lysine levels. It is demonstrated in vitro by an increase in residual ornithine aminotransferase activity in cultured skin fibroblasts when assayed with increased levels of pyridoxal phosphate. Patients who are responsive to vitamin B6 generally have a less severe and more slowly progressive clinical course than patients who are not responsive. Somatic cell hybridization studies have demonstrated absence of complementation among vitamin B6 responsive and nonresponsive forms of gyrate atrophy,[2,3] which indicates that these two forms probably represent different allelic mutants of the same gene.

Because the enzymatic and, in some cases, the genetic defect at the molecular level are known, the histopathologic findings are of particular interest in this disorder. The histopathologic features of the iris,[4] the lens,[5] cultured fibroblasts (James O'Donnell, M.D., oral communication, May 5, 1988), the liver,[6] and skeletal muscle[7-9] have been reported in gyrate atrophy. We studied the light microscopic and ultrastructural findings of the eyes of a patient with well-documented, vitamin B6–responsive gyrate atrophy.

Case Report

A 90-year-old woman was first examined at the Oregon Health Sciences University on Nov. 23, 1979. An intracapsular cataract extraction had been performed on the right eye at the age of 82 years. The patient had an unspecified injury to her left eye as a child. Examination disclosed visual acuity of R.E.: 20/50 with refraction of +10.50 +2.50 × 160 degrees and L.E.: light perception. The kinetic visual field was severely constricted in the right eye to 29 degrees horizontal width with the IV_{4e} test target.[10] Moderate corneal scarring was noted in the left eye. A superior sector iridectomy was noted in the right eye, and moderate atrophy of

Accepted for publication Sept. 28, 1990.

From the Departments of Ophthalmology (Drs. Wilson and Weleber) and Medical Genetics (Dr. Weleber), Oregon Health Sciences University, Portland, Oregon; and Departments of Ophthalmology and Pathology, Johns Hopkins University and Hospital, Baltimore, Maryland (Dr. Green). This study was supported by Medical Research Foundation of Oregon grant 1-2-328-1540 (Dr. Wilson), and a center grant from the National Retinitis Pigmentosa Foundation (Dr. Weleber).

Reprint requests to David J. Wilson, M.D., Department of Ophthalmology, OHSU-L 105, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201.

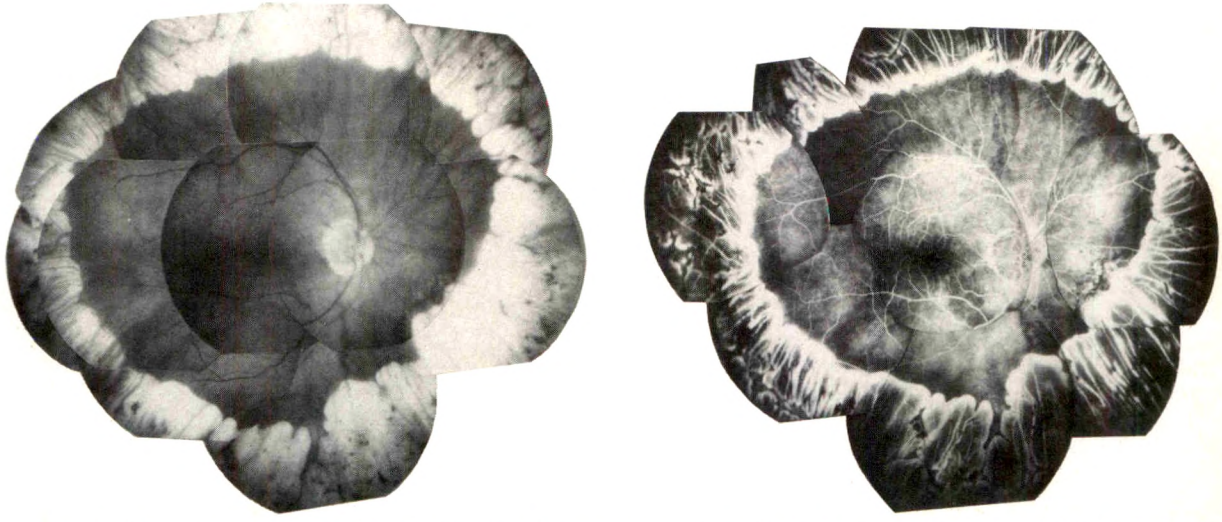


Fig. 1 (Wilson, Weleber, and Green). Fundus photograph (left) and fluorescein angiogram (right) of the right eye.

the iris pigment epithelium was noted in the left eye. The right eye was aphakic, and a mature subluxated cataract was present in the left eye. Ophthalmoscopy disclosed the characteristic appearance of gyrate atrophy (Fig. 1). Fluorescein angiography showed the typical near total loss of choroid and retinal pigment epithelium beyond the posterior pole. The examination included a fasting serum ornithine level of 0.52 mol/ml (normal, 0.083 ± 0.030 mol/ml). A culture of skin fibroblasts was established and used to evaluate the patient's responsiveness to vitamin B6. Activity of ornithine aminotransferase in whole cell extracts was severely deficient at 48 ± 12 nmol/mg of protein per hour (normal mean, 257 nmol/mg of protein per hour; normal range, 152 to 385 nmol/mg of protein per hour), a value which was much higher than that seen in cells of patients who were nonresponsive to vitamin B6 and even higher than that seen in cells from three other patients who were responsive to vitamin B6.[11] Incorporation of radioactivity from ^{3}H-ornithine into protein was 76 ± 9 dpm per gram of protein with no pyridoxine in the media (normal, 638 ± 66 dpm per gram of protein), but 482 ± 91 dpm per gram of protein (normal, 893 ± 134 dpm per gram of protein) when assayed with 1.0 mg of pyridoxine per liter in the assay medium.[11] The ornithine aminotransferase activity in our patient, unlike that in the other three patients who were responsive to vitamin B6, was completely protected from heat lability in the presence of coenzyme.[11] No complementation was exhibited between cells fused with polyethylene glycol among all possible crosses of three patients who were nonresponsive to vitamin B6 and four patients who were responsive (including our patient),[3] which suggests that both groups are allelic.

The patient was examined at intervals before her death at age 98 years on Sept. 11, 1987. There was minimal progression of the retinochoroidal atrophy as assessed by ophthalmoscopy or visual field examination. Visual acuity was 20/40 in the right eye on Sept. 1, 1983, and the patient maintained useful visual acuity until the time of her death. She had a cerebrovascular accident one to two weeks before her death, but the exact cause of death was not determined. The eyes were obtained two hours post mortem (Retinitis Pigmentosa Foundation acquisition number 124) and placed immediately into fixative (phosphate-buffered 1% formaldehyde, 2.5% glutaraldehyde).

Results

The left globe measured 23 (horizontal) × 22 (vertical) × 21 (anteroposterior) mm with corneal diameters of 11.0 × 10.5 mm. Transillumination was increased diffusely. The eye was opened horizontally. The lens was inferiorly subluxated and marked atrophy of the iris pig-

ment epithelium was noted. The ciliary processes were atrophic. Circumscribed patches of retinal pigment epithelial atrophy were noted in the periphery. These became confluent in the fundus midperiphery and then ceased abruptly at the vascular arcades. There was intraretinal perivascular pigment migration in the fundus midperiphery. The retina and retinal pigment epithelium in the posterior pole were unremarkable.

The right globe measured 22 (horizontal) × 22 (vertical) × 23 (anteroposterior) mm and was similar to the left globe, except for surgical aphakia. There was essentially no change in the pattern of chorioretinal atrophy compared to the last clinical photographs. Both globes were processed for light and electron microscopy.

In the left eye, the corneal epithelium was variably thinned and there was nodular scarring of the anterior one third of the corneal stroma. Bowman's layer was absent. Within the area of scarring there were focal aggregates of periodic acid-Schiff stain–positive material that did not stain with Congo red and had the ultrastructural appearance of basement membrane. In both eyes, marked hyalinization of the ciliary processes was noted, but otherwise the ciliary body, iris, and trabecular meshwork were unremarkable. The lens of the left eye was markedly cataractous as evidenced by cortical liquefaction, hyperplasia of the anterior lens epithelium with capsular wrinkling, posterior migration of the lens epithelium, and equatorial calcification of the subepithelial cortex.

In the posterior pole, the retina and retinal pigment epithelium were remarkable for focal areas of photoreceptor cell absence (Fig. 2). Underlying these areas, small clumps of hyperplastic retinal pigment epithelial cells were present. An epiretinal membrane was present, which was thickest overlying the fovea. Temporal to the optic nerve head 8 mm and nasal to the optic nerve head 4 mm, the normal retina and retinal pigment epithelium terminated abruptly. At these locations the retinal pigment epithelium ended, and the photoreceptor cells abutted directly onto Bruch's membrane (Fig. 3). The photoreceptors did not always maintain their proper orientation at this transitional zone, in some cases assuming an orientation tangential to Bruch's membrane. In some areas the choriocapillaris extended a short distance beyond the termination of the retinal pigment epithelium (Fig. 3).

For 2 mm peripheral to this transition zone there was complete absence of the outer retina, retinal pigment epithelium, choriocapillaris, and most of the medium and large choroidal vessels. Peripheral to this zone of near total atrophy, the retinal pigment epithelium was hyperplastic with migration of the pigment epithelium into the retina in a perivascular location. Cross sections of the optic nerve disclosed no optic atrophy.

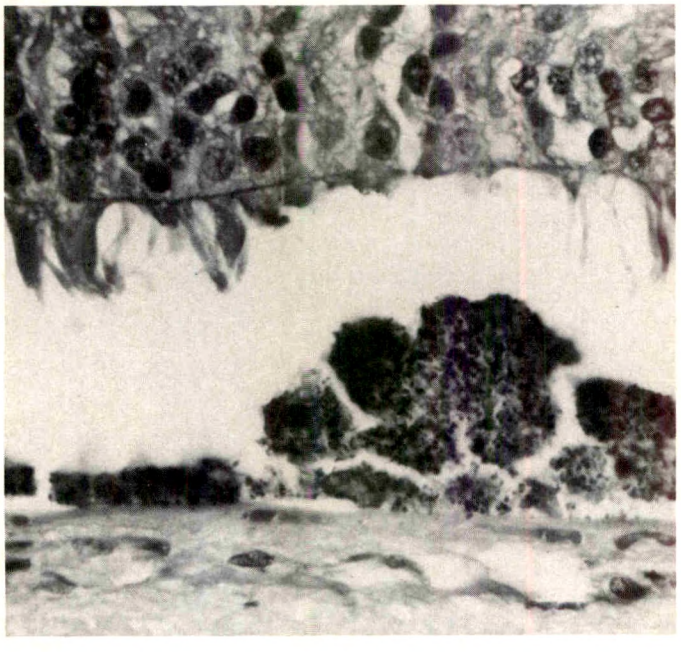


Fig. 2 (Wilson, Weleber, and Green). Focal area of photoreceptor atrophy and adjacent hyperplastic retinal pigment epithelium (periodic acid-Schiff, × 320).

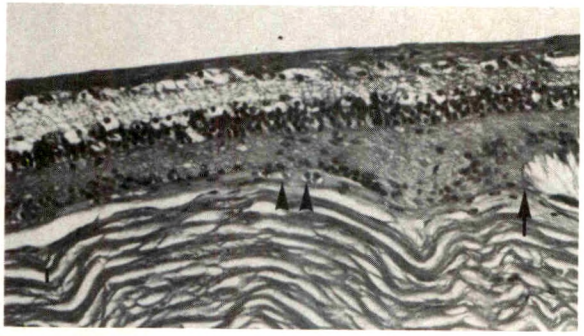


Fig. 3 (Wilson, Weleber, and Green). Abrupt transition from relatively normal retina and pigment epithelium to area with atrophy of the photoreceptor inner and outer segments and retinal pigment epithelium (arrow). In the area of atrophy, the photoreceptor cell nuclei abut directly onto Bruch's membrane. Normal choriocapillaris (arrowheads) extends a short distance into the area of retinal pigment epithelium atrophy (periodic acid-Schiff, × 80).

At the ultrastructural level, striking mitochondrial abnormalities were present within the corneal endothelium and keratocytes of both eyes (Fig. 4). The mitochondria were enlarged with markedly disrupted cristae and electron-lucent matrix. In several mitochondria the cristae were not evident and only fine linear osmiophilic remnants were left in their place (Fig. 4). In other cells the mitochondria were enlarged and the cristae lacked their usual longitudinal orientation. Occasional degenerated endothelial cells were present (Fig. 5). Enlarged mitochondria with electron-lucent matrix were prominent in the nonpigmented and pigmented ciliary epithelium of both eyes (Fig. 6), the smooth muscle of the iris sphincter and ciliary body (Fig. 7), and the striated muscle of the extraocular muscles. Structures resembling tubular aggregates were identified only in the extraocular muscle (Fig. 8), but no classic tubular aggregates were observed.

Similar but markedly less severe mitochondrial abnormalities were present in the photoreceptor inner segments. Dilated mitochondria with relatively electron-lucent matrix were present in the posterior pole but were more common near the areas of chorioretinal atrophy (Fig. 9). These mitochondrial changes were most prominent in the rod ellipsoids but were also present in cone ellipsoids. No mitochondrial abnormalities were present in the retinal pigment epithelium.

In the posterior pole the retinal pigment epithelium–photoreceptor relationships were well maintained (Fig. 10). The retinal pigment epithelium in this region was cuboidal with basal plasmalemmal infoldings and apical microvilli. Near the transition from relatively normal to atrophic retina, the photoreceptor outer segments shortened and eventually disappeared (Fig. 9). In some transitional areas the retinal pigment epithelium was flattened, contained fewer pigment granules, and lost its apical microvilli and basal infoldings (Fig. 11). In other areas the retinal pigment epithelium maintained a fairly cuboidal and polarized structure (Fig. 9). The polarized cuboidal structure was preserved principally in areas where the retinal pigment epithelium maintained contact with photoreceptor inner or outer segments. In the 2-mm zone of extreme atrophy, glial cells abutted directly onto Bruch's membrane and in one area extended into the choroid.

Discussion

The extensive clinical documentation of this case permits several interesting clinicopathologic correlations. In making these correlations it is important to note that this patient was remarkably responsive to vitamin B6, and other patients nonresponsive and responsive to vitamin B6 with gyrate atrophy might differ significantly.

Except for the focal areas of photoreceptor atrophy and mitochondrial abnormalities, the photoreceptors and retinal pigment epithelium in the posterior pole were unremarkable. These areas of focal photoreceptor atrophy differ from those described in autosomal dominant vitreochoroidopathy by Goldberg and associates.[12] The underlying retinal pigment epithelium was hyperplastic in our case rather than atrophic as described in autosomal dominant vitreochoroidopathy.[12] An epiretinal membrane was present in each eye, and this finding has been described clinically in patients with gyrate atrophy.[1] Slightly peripheral to the relatively normal retina was a zone of marked atrophy with almost complete absence of the medium and large choroidal vessels, the choriocapillaris, and the outer retina. The retinal pigment epithelium in this area was either totally absent or consisted of spindle-shaped cells, with little intracytoplasmic pigment and without the polarity characteristic of normal retinal pigment epithelium. At the transition between these two

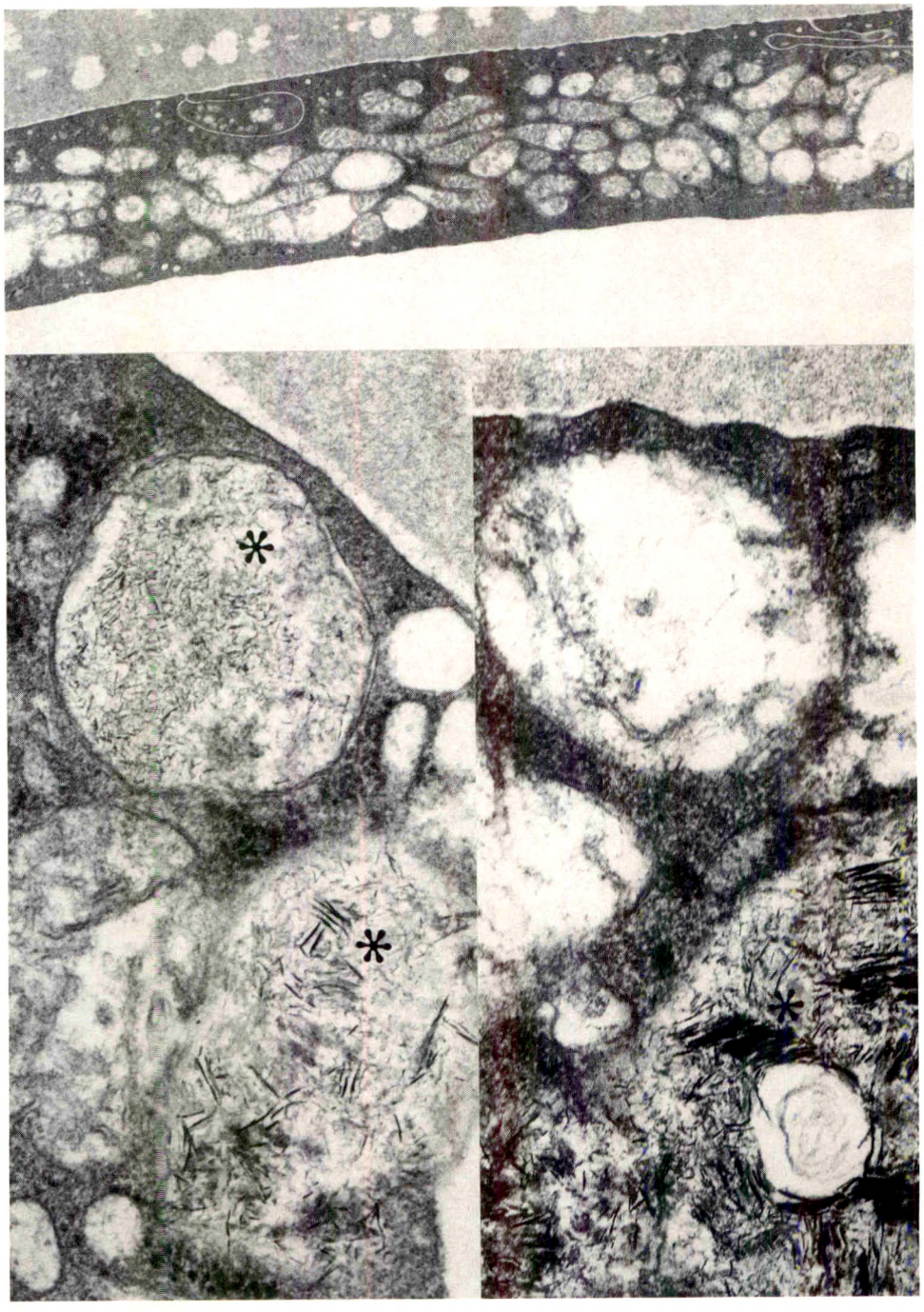


Fig. 4 (Wilson, Weleber, and Green). Top, Marked swelling of the inner compartment of the mitochondria of the corneal endothelium. Bottom left and bottom right, The cristae are markedly disrupted with only fine markedly osmophilic remnants (asterisk) remaining in some areas (× 60,000).

zones, the retinal pigment epithelium in contact with photoreceptor outer or inner segments tended to maintain its normal configuration, whereas the retinal pigment epithelium without this contact assumed the spindle structure. The choriocapillaris extended a short distance into the atrophic area, which suggests that choriocapillaris atrophy may be secondary to retinal pigment epithelial atrophy. This is analogous to the secondary choriocapillaris at-

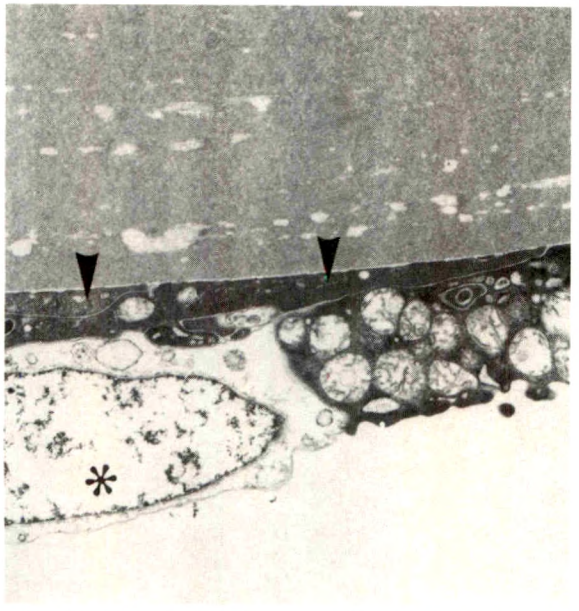


Fig. 5 (Wilson, Weleber, and Green). Degenerated endothelial cell (asterisk) separated from Descemet's membrane by intact endothelial cells (arrowheads) (× 6,800).

rophy observed after retinal pigment epithelial injury in experimental animals.[13]

The most prominent ultrastructural abnormality we observed were the abnormal mitochondria in the corneal endothelium, smooth muscle of the iris and ciliary body, the ciliary body epithelia, and to a lesser extent in the photoreceptors. This feature has been observed in the skeletal muscle,[7-9] liver,[6] iris,[4] and cultured fibroblasts (James O'Donnell, M.D., oral communication, May 5, 1988) of patients with gyrate atrophy.

The most severe mitochondrial abnormalities were present in the corneal endothelium and nonpigmented ciliary body epithelium. Occasional necrotic endothelial cells were present, but there was no clinical indication that these tissues were adversely affected by the mitochondrial changes. The corneal scarring present in the left eye was probably a result of the injury the patient sustained in childhood. Conversely, the least severe mitochondrial abnormalities were present in the retina, and none were observed in the retinal pigment epithelium, the tissues most severely affected in gyrate atrophy. It is possible, however, that more severe mitochondrial abnormalities were present in the portion of the retina and retinal pigment epithelium that had degenerated previously.

Enlarged mitochondria with electron-lucent matrices have been described in various types of cell injury and are caused by an influx of water into the inner compartment of the mitochondria.[14] They may also be seen because of delayed fixation or when low concentrations of glutaraldehyde (less than 1%) are used as a single fixative[15]; but neither of these circumstances were present in our case.

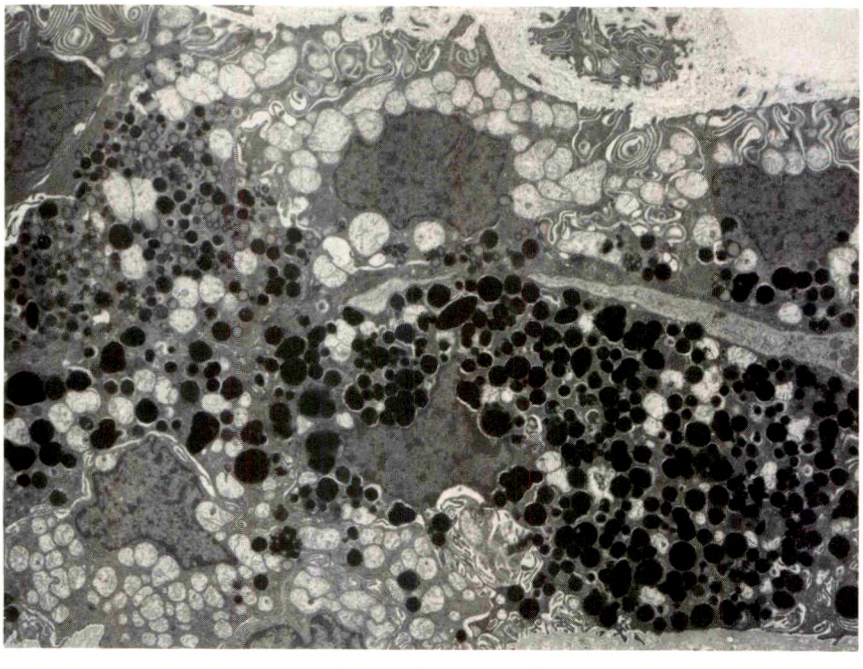


Fig. 6 (Wilson, Weleber, and Green). Top, Marked swelling of mitochondria in nonpigmented and pigmented ciliary epithelium (× 2,800).



Fig. 7 (Wilson, Weleber, and Green). Enlarged and swollen mitochondria with distorted cristae (arrowheads) in smooth muscle of the iris (× 16,000).

Since ornithine aminotransferase is a mitochondrial enzyme, it is possible that local abnormalities of intramitochondrial metabolites result in mitochondrial swelling under fixation and processing conditions that normally do not alter mitochondrial structure. However, the well-preserved, normal mitochondria in adjacent ocular tissues would suggest the mitochondrial changes are not purely fixation artifact.

Since it is unlikely that the mitochondrial changes are purely artifactitious, theories as to the pathophysiologic characteristics of gyrate atrophy should explain these changes and their distribution. Valle and Simell[16] reviewed the possible biochemical mechanisms of chorioreti-

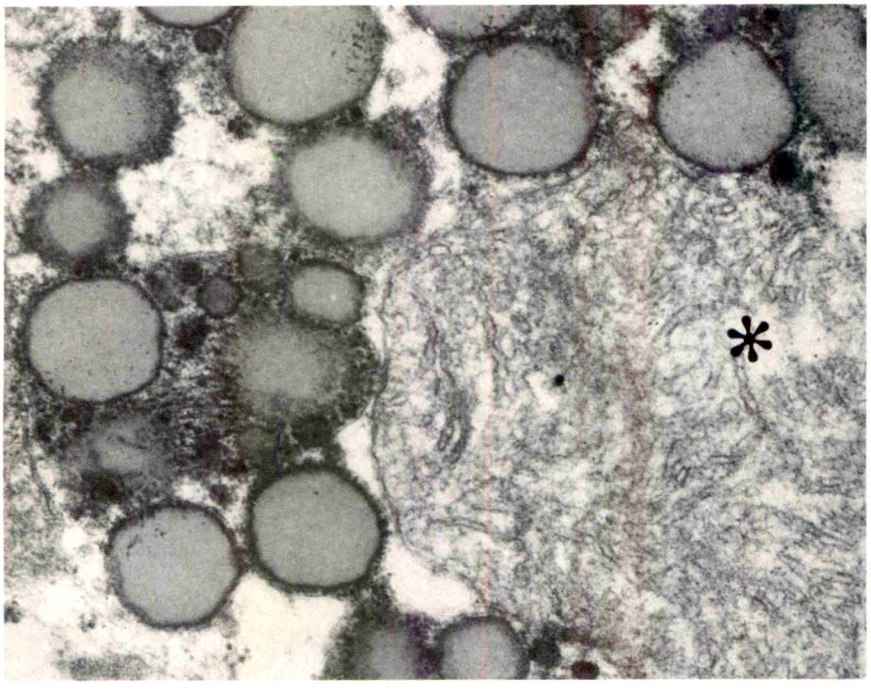


Fig. 8 (Wilson, Weleber, and Green). Tubular membranous structures (asterisk) with some similarity to the tubular aggregates seen in skeletal muscle biopsy specimens of patients with gyrate atrophy. A large amount of lipofuscin is also present (× 42,000).

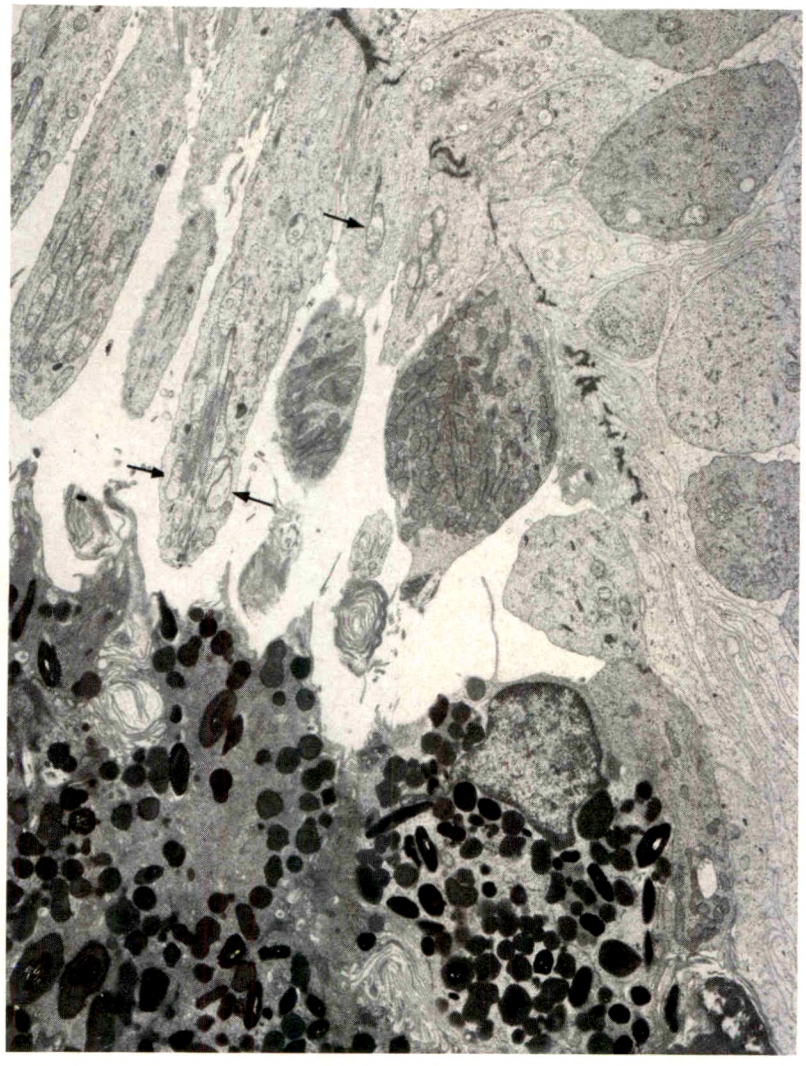


Fig. 9 (Wilson, Weleber, and Green). Retina at junction between relatively normal and atrophic areas. Some mitochondria with electron-lucent matrices and distorted cristae are present in the rod inner segments (arrows). No similar changes are present in the retinal pigment epithelium (× 3,400).

nal degeneration in gyrate atrophy. It is unlikely that hyperornithinemia alone is the cause of the chorioretinal degeneration, as this feature is not present in other diseases with hyperornithinemia.[16,17]

Based on the known biochemical abnormalities in gyrate atrophy, Valle and Simell[16] maintained that two nonexclusive biochemical mechanisms for the degeneration seem most plausible. The first involves the inhibition of the extramitochondrial arginine-glycine transamidinase pathway by the increased ornithine levels, resulting in deficiency of production of creatine phosphate. Relatively little is known about the role of creatine phosphate as an essential energy store for the retina. Walliman and associates[18] have shown high concentrations of creatine kinase and creatine phosphate in rod and cone photoreceptor cells. Immunofluorescent studies of the two isoforms of creatine kinase localized the brain isoform to the inner segment of both rod and cone photore-

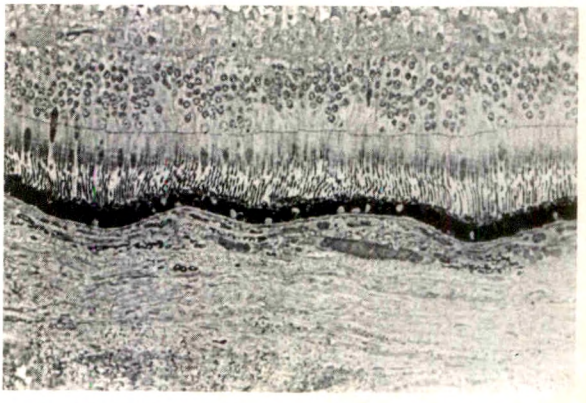


Fig. 10 (Wilson, Weleber, and Green). Low-power photomicrograph of photoreceptors and retinal pigment epithelium in the posterior pole (× 120).

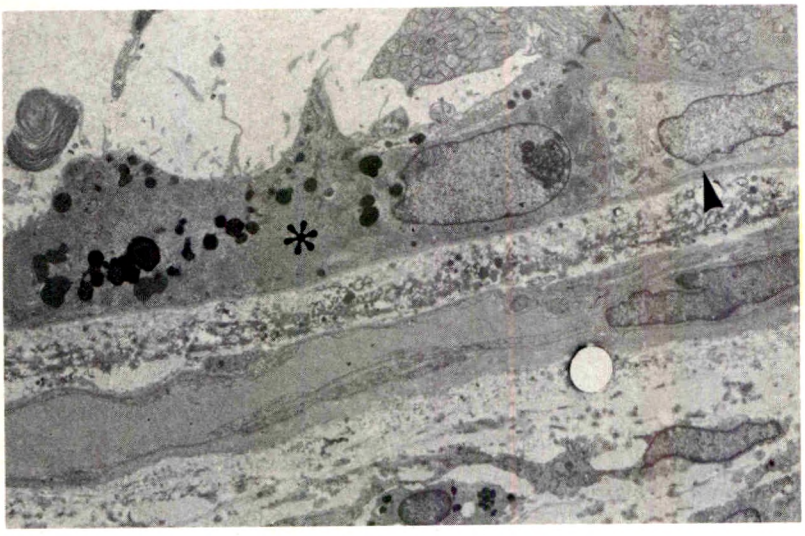


Fig. 11 (Wilson, Weleber, and Green). Transition from pigmented polarized retinal pigment epithelium (asterisk) to depigmented spindle-shaped retinal pigment epithelium (arrowhead) is abrupt and occurs where the retinal pigment epithelium loses contact with the photoreceptor inner and outer segments (×2,800).

ceptors and the mitochondrial isoform to the ellipsoid of the inner segments of the photoreceptors.

The second proposed mechanism for the chorioretinal degeneration involves deficient production of delta^1-pyrroline-5-carboxylate secondary to the deficiency of ornithine aminotransferase and to the inhibitory effects of ornithine on the enzyme delta^1-pyrroline-5-carboxylate synthase. Deficient production of delta^1-pyrroline-5-carboxylate results in decreased proline synthesis and disrupts the regulatory roles of delta^1-pyrroline-5-carboxylate and its metabolic interconversions on the intracellular redox level and hexose monophosphate shunt activity.

Maintenance of a low mitochondrial water content is dependent on normal mitochondrial adenosine triphosphate production[19] and the osmotic forces across the mitochondrial membranes. Since both delta^1-pyrroline-5-carboxylate and creatine phosphate are potentially involved with the chemiosmotic mechanism of mitochondrial adenosine triphosphate production, which secondarily affects mitochondrial water homeostasis, it is possible that deficiency of either or both of these biochemical compounds could cause the mitochondrial swelling. Alternatively, accumulation of osmotically active metabolites within the mitochondria could result in mitochondrial swelling on an osmotic basis.

Other diseases with known defects of mitochondrial energy metabolism, such as Kearns-Sayre syndrome or cytochrome oxidase deficiency, have distinct abnormalities of mitochondrial structure. Mitochondrial swelling, however, is not a feature of those disorders.

It is still unclear what role mitochondrial swelling played in the chorioretinal degeneration, as only minor mitochondrial swelling was present in the photoreceptors. The most severe mitochondrial changes were present in the corneal endothelium and nonpigmented ciliary epithelium, tissues that do not manifest any clinical abnormalities in gyrate atrophy. It may be that the prominent ultrastructural abnormalities of the mitochondria are not detrimental to the involved cells.

It is always difficult to determine from the study of postmortem tissue whether the photoreceptors or retinal pigment epithelium cells are the primary cells involved in a retinal dystrophy. We did find abnormalities of the mitochondria of the photoreceptors that were not present in the retinal pigment epithelium. Furthermore, in the relatively intact posterior pole, focal areas of photoreceptor atrophy were found in association with hyperplastic retinal pigment epithelium. We think both these findings are more suggestive of a primary photoreceptor abnormality than a retinal pigment epithelial defect.

References

1. Weleber, R. G., and Kennaway, N. G.: Gyrate atrophy of the choroid and retina. In Heckenlively, J. R. (ed.): Retinitis Pigmentosa. Philadelphia, J. B. Lippincott, 1988, pp. 198–220.

2. Shih, V. E., Mandell, R., Jacoby, L. B., and Berson, E. L.: Genetic complementation analysis in fibroblasts from gyrate atrophy and the syndrome of hyperornithinemia, hyperammonemia, and homocitrullinuria. Pediatr. Res. 15:569, 1982.

3. Wirtz, M. K., Kennaway, N. G., and Weleber, R. G.: Heterogeneity and complementation analysis of vitamin B6 responsive and nonresponsive patients with gyrate atrophy of the choroid and retina. J. Inherited Metab. Dis. 8:71, 1985.

4. Vannas-Sulonen, K., Vannas, A., O'Donnell, J. J., Sipila, I., and Wood, I.: Pathology of iridectomy specimens in gyrate atrophy of the retina and choroid. Acta Ophthalmol. 61:9, 1983.

5. Kaiser-Kupfer, M., Kuwabara, T., Uga, S., Takki, K., and Valle, D.: Cataract in gyrate atrophy. Clinical and morphologic studies. Invest. Ophthalmol. Vis. Sci. 24:432, 1983.

6. Arshinoff, S. A., McCulloch, J. C., Matuk, Y., Phillips, M. J., Gordon, B. A., and Marliss, E. B.: Amino-acid metabolism and liver ultrastructure in hyperornithinemia with gyrate atrophy of the choroid and retina. Metabolism 28:979, 1979.

7. McCulloch, J. C., and Marliss, E. B.: Gyrate atrophy of the choroid and retina with hyperornithinemia. Am. J. Ophthalmol. 80:1047, 1975.

8. Sipila, I., Simell, O., Rapola, J., Sainio, K., and Fuuteri, L.: Gyrate atrophy of the choroid and retina with hyperornithinemia. Tubular aggregates and type 2 fiber atrophy in muscle. Neurology 29:996, 1979.

9. Shapira, Y., Yatziv, S., Merin, S., Statler, M., and Yarom, R.: Myopathy in hyperornithemic gyrate atrophy of choroid and retina. Isr. J. Med. Sci. 17:271, 1981.

10. Weleber, R. G., Wirtz, M. K., and Kennaway, N. G.: Gyrate atrophy of the choroid and retina. Clinical and biochemical heterogeneity and response to vitamin B6. Birth Defects 18:219, 1982.

11. Kennaway, N. G., Stankova, L., Wirtz, M. K., and Weleber, R. G.: Gyrate atrophy of the choroid and retina. Characterization of mutant ornithine aminotransferase and mechanism of response to vitamin B6. Am. J. Hum. Genet. 44:344, 1989.

12. Goldberg, M. F., Lee, F., Tso, M. O. M., and Fishman, G. A.: Histopathologic study of autosomal dominant vitreochoroidopathy. Ophthalmology 96:1736, 1989.

13. Korte, G. E., Gerszberg, T., Pua, F., and Henkind, P.: Choriocapillaris atrophy after experimental destruction of the retinal pigment epithelium in the rat. A study in thin sections and vascular casts. Acta Anat. 127:171, 1986.

14. Ghadially, F. N.: Ultrastructural Pathology of the Cell and Matrix, ed. 2. London, Butterworths, 1982, pp. 196–203.

15. Romert, P., and Matthiessen, M. E.: Swelling of mitochondria in immersion-fixed liver tissue. Effects of various fixatives and of delayed fixation. Acta Anat. 109:332, 1981.

16. Valle, D., and Simell, O.: The hyperornithinemias. In Scriver, C. R., Beandet, A. L., Sly, W. S., and Valle, D. (eds.): The Metabolic Basis of Inherited Disease. New York, McGraw-Hill, 1989, pp. 599–627.

17. Shih, V. E., Efron, M. L., and Moser, H. W.: Hyperornithinemia, hyperammonemia, and homocitrullinuria. A new disorder of amino acid metabolism associated with myoclonic seizures and mental retardation. Am. J. Dis. Child. 117:83, 1969.

18. Walliman, T., Wegmann, G., Moses, H., Huber, R., and Eppenberger, H. M.: High content of creatine kinase in chicken retina. Compartmentalized localization of creatine kinase isoenzymes in photoreceptor cells. Proc. Natl. Acad. Sci. U.S.A. 83:3816, 1986.

19. Laiho, K. U., Shelburne, J. D., and Trump, B. F.: Observations on cell volume, ultrastructure, mitochondrial conformation and vital dye uptake in Ehrlich ascites tumor cells. Am. J. Pathol. 65:203, 1971.

OPHTHALMIC MINIATURE

His eyes had a starey look, somewhat like the eyes of people who wear glasses when they have their glasses off.

John D. MacDonald, *Pale Gray for Guilt*
New York, Ballantine Books, 1968, p.23

Signs, Complications, and Platelet Aggregation in Familial Exudative Vitreoretinopathy

C. Erik van Nouhuys, M.D.

Between 1979 and 1989, I examined 106 patients (16 pedigrees) with signs of familial exudative vitreoretinopathy. Of these patients, 101 had familial exudative vitreoretinopathy, and five had a sporadic manifestation. The complications of familial exudative vitreoretinopathy, deformation of the posterior retina, vitreous hemorrhage, amblyopia, and retinal detachment, caused diminished visual acuity. Of 170 eyes, retinal neovascularization was observed in 18 eyes (11%), and retinal exudates were observed in 16 eyes (9%). Several forms of retinal detachment occurred in 37 of 180 eyes (21%), which often took an unfavorable course. A falciform retinal fold was observed in 14 eyes (8%). Retinal surgery was performed in 14 eyes; reattachment of the retina was successful in only seven eyes. Platelet aggregation studies disclosed no significant differences between seven patients with familial exudative vitreoretinopathy and ten control subjects. The pathogenesis of the disease is based on a premature arrest of the vascular development of the retina.

FAMILIAL EXUDATIVE VITREORETINOPATHY (also known as dominant exudative vitreoretinopathy) is a hereditary disorder with autosomal dominant transmission characterized by a boundary of the retinal vascular network in the equatorial region of the fundus and avascularity of the peripheral retina, especially on the temporal side. More severely affected eyes show a variety of signs, such as deformation of the posterior retina, ectopia of the macula, retinal neovascularization and exudates, pigmentary changes of the retina, retinal breaks, vitreous hemorrhages and membranes, retinoschisis, retinal detachment, cataract, band-shaped keratopathy, and phthisis bulbi.[1-8]

The fundus abnormalities of familial exudative vitreoretinopathy are similar to those of retinopathy of prematurity. Therefore, retinopathy of prematurity can be regarded as a phenocopy of familial exudative vitreoretinopathy.[8,9]

Because of its frequently asymptomatic course and the diversity of signs, the disease is often unrecognized or diagnosed incorrectly. The purpose of this study was to describe and catalog the various signs and complications of the disease as well as their prevalence in a relatively large group of patients.

Chaudhuri and associates[10] reported disturbed platelet aggregation in seven patients with familial exudative vitreoretinopathy. In view of these findings, I performed a controlled study of platelet aggregation in 17 patients.

Patients and Methods

Between 1979 and 1989, I examined Dutch families with familial exudative vitreoretinopathy at the Eye Clinic of the University of Nijmegen and at the Canisius-Wilhelmina Hospital. Generally, familial exudative vitreoretinopathy was diagnosed after biomicroscopic observation of the characteristic equatorial demarcation between vascular and avascular retina and the angiographic finding of nonperfusion of the peripheral retina.

Ophthalmic examinations of 350 patients showed characteristics of familial exudative vitreoretinopathy in 106 patients. The disease was familial in 101 patients from 16 pedigrees. In 11 of these patients, the vascular lesions of the peripheral retina were so slight that the diagnosis could not be confirmed with absolute cer-

Accepted for publication Oct. 15, 1990.

From the Department of Ophthalmology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands. This study was supported in part by the Praeventiefonds, The Hague, The Netherlands.

Reprint requests to C. Erik van Nouhuys, M.D., Department of Ophthalmology, Canisius-Wilhelmina Hospital, P.O. Box 9015, 6500 GS Nijmegen, The Netherlands.

tainty. The data of these 11 patients are not included. The remaining 90 patients in the 16 pedigrees showed evident signs of the disease. Five of these patients, including identical twins, showed unmistakable ocular lesions, although no signs of familial exudative vitreoretinopathy could be found in their immediate family. As such sporadic cases may result from genetic heterogeneity, the data on these patients are not included. All patients with familial and sporadic exudative vitreoretinopathy had a birthweight over 2,000 g, and none were premature. Three patients had been given some supplemental oxygen immediately after birth for one or two days.

In all patients, the ophthalmic examination included determination of visual acuity, determination of the eye position and kappa angle, and slit-lamp examination of the anterior segment. Patients were questioned regarding any previous ocular diseases and neonatal details. Ophthalmoscopy was always performed in full mydriasis after instillation of 0.5% tropicamide, 5% phenylephrine, and sometimes 1% cyclopentolate eyedrops. In all older children and adults, the fundus was examined by biomicroscopy with a three-mirror contact lens. For young children, ophthalmoscopy was considered sufficient. Fluorescein angiography and color photography of the peripheral fundus and posterior pole were performed in selected patients. In a few of the patients, kinetic perimetry (Goldmann), scotopic and photopic electroretinography, and electro-oculography were performed.

Hematologic tests and platelet aggregation tests were performed in seven patients with unmistakable familial exudative vitreoretinopathy in three pedigrees and in ten age-matched control subjects.

For the platelet aggregation tests, citrated blood from patients and control subjects was used to prepare platelet-rich plasma by centrifugation on a cushion for 20 minutes at 250 G.[11] Aggregation in platelet-rich plasma was measured with a photometer. Aggregation was induced with adenosine diphosphate diluted to end-concentrations of 10^{-6} mol/l, 4×10^{-7} mol/l, and 2×10^{-7} mol/l; collagen suspensions in 0.9% sodium chloride (2×10^{-5} l and 5×10^{-6} l); and arachidonic acid (end concentrations of 5×10^{-3} mol/l and 1.5×10^{-3} mol/l). The bleeding time was determined in five patients and ten control subjects. This was done after placing a sphygmomanometer cuff on the upper arm and inflating it to 40 mm Hg, using a bleeding-time device.

Results

Visual acuity was determined in 176 eyes of 90 patients with evident familial exudative vitreoretinopathy (the patients with minimal fundus lesions and nonfamilial exudative vitreoretinopathy were excluded). Whenever visual acuity was determined more than once in the same individual, the most recent value was recorded. Of 176 eyes, visual acuity was 20/20 or better in 65 eyes (37%); 20/35 to 20/25 in 48 eyes (27%); 20/70 to 20/40 in 14 eyes (8%); 20/200 to 20/100 in 12 eyes (7%); counting fingers in 17 eyes (10%); hand motions in seven eyes (4%); and no light perception in 15 eyes (9%). Determined binocularly, visual acuity was 20/100 or less in 13 of 88 patients (15%).

In 180 eyes of 90 patients with familial exudative vitreoretinopathy, the vitreous was normal in 80 eyes (44%); syneresis and liquefaction were noted in 42 eyes (23%); delicate white particles were seen in 27 eyes (15%); pigmented cells were noted in nine eyes (5%); vitreous hemorrhage occurred in four eyes (2%); preretinal membranes and opacities were seen in 30 eyes (17%); membranes in various parts of the vitreous were seen in 25 eyes (14%). In 12 eyes, clinical or histologic examination disclosed extensive retrolental organizations in combination with total retinal detachment and often with secondary lesions of the anterior segment and atrophy of the entire globe (Fig. 1).

A solid local fibrovascular mass of tissue was observed in ten eyes (6%). Without exception this mass was localized in the temporal or inferotemporal part of the fundus periphery and was linked to the local retina, the ciliary body, and the peripheral part of the posterior lens capsule. In most cases, a fixed falciform retinal fold had developed in association with this lesion.

Avascularity of the peripheral retina and the typical demarcation by the border of aberrant terminal ramifications of the retinal vessels in the region of the temporal equator were observed in 135 of 170 eyes (79%) (Fig. 2). The configuration of the retinal vessels central to this marginal zone was often aberrant. In other studies of familial exudative vitreoretinopathy, this region showed an abnormally large number of vascular ramifications in which the course showed an abnormally parallel orientation.[2,6,12] A configuration of this type was seen in 108 of 170 eyes (64%) in the present series.

Neovascularizations were found in 18 of 170 eyes (11%) with familial exudative vitreoreti-

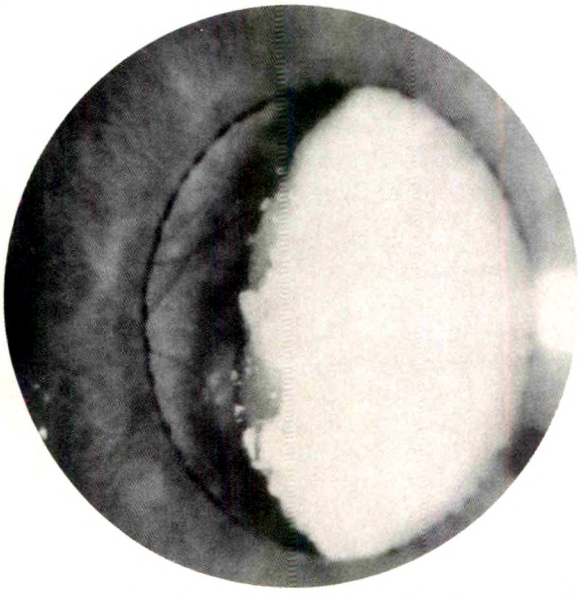


Fig. 1 (van Nouhuys). Left eye of a 25-year-old man. The anterior segment shows a totally cataractous lens with a highly vascularized mass of fibrous tissue visible behind it.

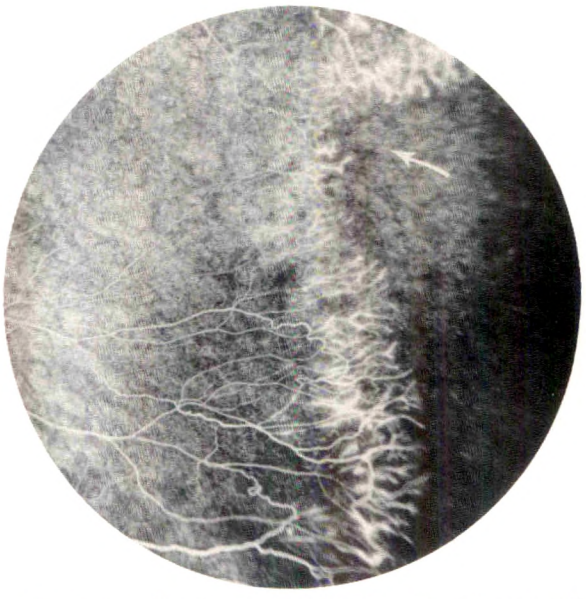


Fig. 2 (van Nouhuys). Left fundus of a 17-year-old girl. Fluorescein angiogram (venous phase) of the temporal equator region shows the typical configuration of retinal vessels of familial exudative vitreoretinopathy. The peripheral retina is avascular and shows a V-shaped notch between the terminal ramifications of the superotemporal and inferotemporal vessels (arrow).

nopathy; these usually developed from the most peripheral retinal vascular ramifications on the temporal side of the fundus. The activity of these neovascularizations differed considerably. In children, the vessels sometimes showed a vital appearance with a red color, incidental local bleeding in or in front of the retina was seen, or growth was observed. In older children and adults, the neovascularizations were usually fibrotic, although fluorescein angiography disclosed perfusion and leakage of the dye (Figs. 3 and 4).

Ectopia of the macula, ranging from hardly perceptible to pronounced, was observed in 83 of 170 eyes (49%). The macular displacement was always temporal or inferotemporal.

As other studies[13,14] have shown, exudates were fairly uncommon, occurring in 16 of 170 eyes (9%). They were usually small intraretinal exudates in the region of the temporal equator, but massive subretinal exudates were incidentally observed (Fig. 5). Other fundus changes included the following: tortuous retinal veins in 56 eyes (33%); deformation of posterior retina in 101 eyes (59%); dragged optic disk in 16 eyes (9%); retinal pigmentation in 35 eyes (21%); retinal hemorrhages in two eyes (1%); retinal defects in 19 eyes (11%); white changes of peripheral retina in 37 eyes (22%); and atrophic changes of choroid and retinal pigment epithelium in 39 eyes (23%).

In 37 of 180 eyes (21%) with evident familial exudative vitreoretinopathy, retinal detachment occurred once or several times or a preexisting retinal detachment was found. Eight of 180 eyes (4%) showed retinoschisis, which was always limited to a segment of the peripheral retina.

Recent rhegmatogenous retinal detachment was observed in nine of the 37 eyes with retinal detachment. The retinal defects in this group were widely diverse, including small round holes, horseshoe-shaped tears, and even giant tears (Fig. 6). Ten eyes had become blind before first examination because of chronic total retinal detachment. Two eyes in this group were subjected to light microscopic examination, which disclosed extensive lesions of the type observed histologically in the terminal stage of a proliferative retinopathy. The pathologic features of one specimen were previously reported,[8] and these features corresponded with the microscopic findings of other studies.[15-17]

Fourteen eyes showed a falciform retinal fold. In all of these eyes, a prominent fold extended from the optic disk through the posterior pole to the temporal or inferotemporal periphery of the fundus (Fig. 7). I observed several of these falciform retinal folds over a period of more than five years, without any change in the

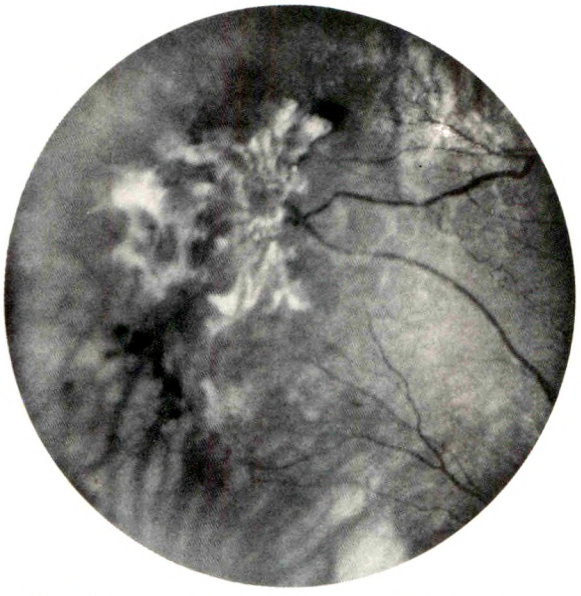


Fig. 3 (van Nouhuys). Right fundus of a 5-year-old girl. The temporal equator region shows partly fibrotic new vessels and a few minor retinal hemorrhages.



Fig. 4 (van Nouhuys). Right fundus of a 33-year-old woman. Fluorescein angiogram shows leakage of dye from an equatorial neovascularization. The new vessels were chronic and partly fibrotic.

position of the retina. In the eye of a young girl, however, the formation of a falciform retinal fold could be observed. Another child with bilateral falciform retinal folds showed gradual progression toward a total funnel retinal detachment in one eye. Most falciform retinal folds developed at preschool age, and a few were observed within a few months of birth.

Only one eye showed a purely exudative retinal detachment, and biomicroscopy disclosed no retinal defects in this eye. In another eye with total, mainly tractional retinal detach-

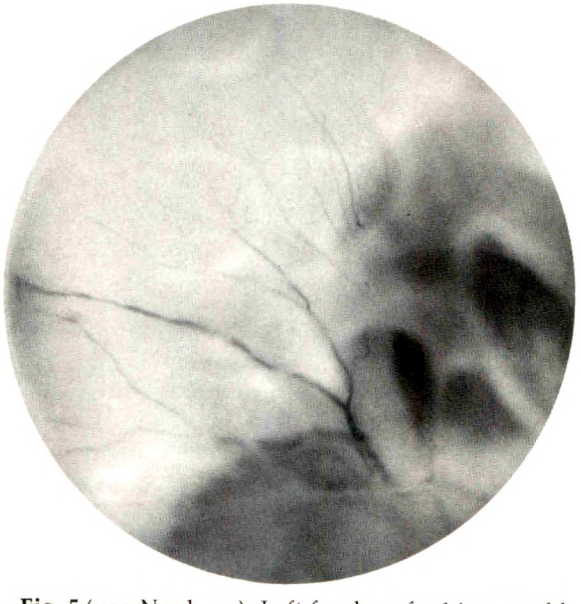


Fig. 5 (van Nouhuys). Left fundus of a 14-year-old girl. A large subretinal exudate is visible in the nasal upper quadrant. Note the preretinal membranes.

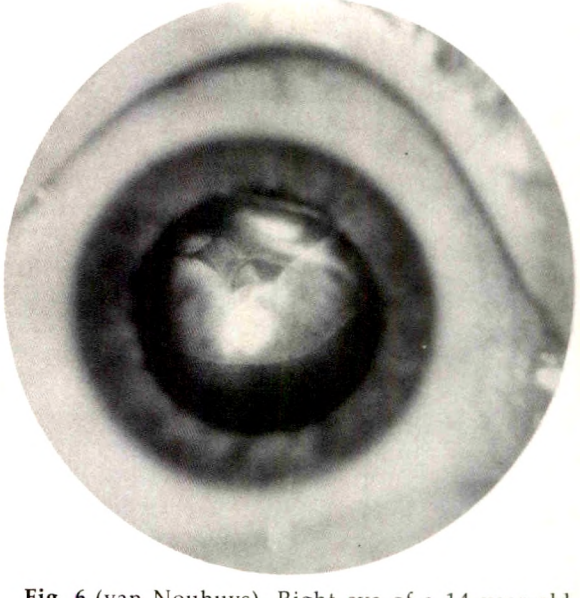


Fig. 6 (van Nouhuys). Right eye of a 14-year-old girl. Detached retina with a giant tear on the superior side.

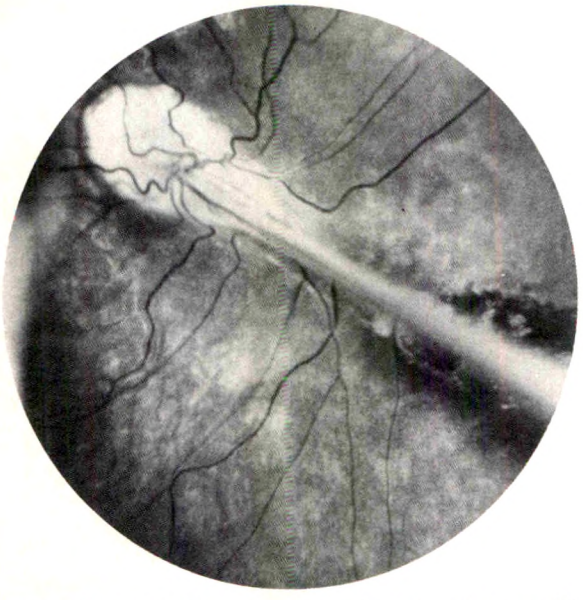


Fig. 7 (van Nouhuys). Left fundus of a 30-year-old woman. Falciform retinal fold extending from the optic disk across the posterior pole to the inferotemporal periphery.

ment, however, extensive subretinal exudates were found (Fig. 5).

Retinal detachment surgery was performed in 14 eyes (12 eyes of patients with familial exudative vitreoretinopathy and two eyes of a patient with sporadic exudative vitreoretinopathy). The surgery was done in different hospitals by different ophthalmic surgeons and included scleral buckling operations (eight eyes), pars plana vitrectomy with or without scleral buckles (six eyes), pars plana vitrectomy with silicone oil (six eyes), removal of subretinal silicone oil (one eye), and removal of sponges (one eye). A total of 22 retinal operations were performed.

Surgery was performed in patients with rhegmatogenous retinal detachment with or without signs of proliferative vitreoretinopathy, tractional retinal detachment without visible breaks, and exudative retinal detachment. One eye underwent a vitrectomy because of progression of traction on an attached retina.

Seven operations (two vitrectomies and five scleral buckling procedures) were successful (reattachment during at least six months after the operation); 13 operations (ten vitrectomies and three scleral buckling procedures) were not successful (nonattachment or redetachment within six months after the operation). In eight eyes the first operation was not successful, and six eyes required more than one operation.

Reattachment of the retina in one or more procedures was successful in seven eyes. The age of the patients in this group at the time of operation ranged from 19 to 56 years (mean, 30 years). The retinas of the other seven eyes could not be repositioned. The age of these patients at the time of surgery ranged from 5 to 18 years (mean, 13 years).

The platelet aggregation test results are listed in the Table. For each aggregation inducer, the mean and the standard deviation of the number of aggregation units determined photometrically in the patient group and in the control group were compared. Using adenosine diphosphate in three different concentrations, no significant difference was found between the patient group and the control group ($P = .27$, $.52$, and $.70$, respectively). Using 1.5 mmol/l of arachidonic acid, no significant difference was found ($P = .22$). With 5 mmol/l of arachidonic acid, however, platelet aggregation in the patient group was found to exceed that in the control group ($P = .003$). With 5×10^{-6} l of collagen as inducer, there was no significant difference ($P = .52$), but with 2×10^{-5} l of collagen, a slightly lower aggregation was found in the patient group; however, the difference was not significant ($P = .04$). The bleeding time averaged 538 seconds (standard deviation, 67 seconds) in five patients, compared with 522 seconds (standard deviation, 157 seconds) in ten control subjects. These values did not differ significantly.

Discussion

Although familial exudative vitreoretinopathy may lead to blindness at an early age, most of the gene carriers showed no severe visual handicap. The course of the visual function tests during the period of observation confirmed the postulate that the disease is not a gradually progressive degeneration, as some researchers believe. When visual acuity was diminished, it was a result of complications. The following complications may lead to diminished visual acuity: deformation of the macula because of traction or edema, vitreous hemorrhage, retinal detachment, and, in young children, amblyopia.[8,18,19] Amblyopia as a complication of familial exudative vitreoretinopathy has rarely been reported, but probably is not uncommon.[8] Amblyopia, usually combined with considerable anisometropia, played a role in the diminished visual acuity of 12 (13%) of my patients.

In 80 of 180 (44%) eyes, no vitreous lesions were observed. Pronounced vitreous membranes were almost exclusively seen in eyes with an extensive retinopathy or in eyes with chronic retinal detachment. These findings seem to warrant the conclusion that the vitreous changes in familial exudative vitreoretinopathy results from the vasculopathy and its complications, such as retinal neovascularizations and vitreous hemorrhages. Chronic leakage of blood constituents from retinal vessels may also induce fibrous proliferation in the preretinal vitreous, as Machemer[20] suggested.

The vascular lesions of the peripheral retina in familial exudative vitreoretinopathy have been frequently described.[3,5,6,13,21] The avascularity of the peripheral retina and the typical demarcation by the equatorial zone of aberrant terminal ramifications of retinal vessels were observed biomicroscopically in 135 of 170 eyes (79%). In familial exudative vitreoretinopathy, the marginal zone of peripheral vascular branches frequently shows a V-shaped notch near the temporal horizontal meridian (Fig. 2).[8,12] Miyakubo, Hashimoto, and Miyakubo[13] found this configuration in 108 (81%) of the eyes in their series, and regarded the anomaly as one of the principal characteristics of familial exudative vitreoretinopathy.

It is extremely interesting to compare this configuration with the normal human fetal retina during the final two to three months of the intrauterine period. The flat specimen of the normal fetal retina in this stage shows a V-shaped marginal zone of immature vascular tissue,[22] which is identical with the configuration of the border zone in the mature eye in familial exudative vitreoretinopathy. This morphologic similarity supports the postulate that the pathogenesis of this disease is based on premature arrest of the vascular development of the retina. In view of the state of development of the retinal vascularization in the fundus in familial exudative vitreoretinopathy, this arrest cannot have occurred before the seventh month of the intrauterine period.

The relationship between familial exudative vitreoretinopathy and falciform retinal fold has been discussed.[23-26] Fourteen cases of falciform retinal fold were found in families with familial exudative vitreoretinopathy, which shows that familial exudative vitreoretinopathy is an important and probably by far the most frequent cause of falciform retinal fold in patients who otherwise show no general congenital anomalies.

These observations are important, not only for the classification of the congenital retinal fold syndrome but also because they provide information about the pathogenesis of this condition.

TABLE

PLATELET AGGREGATION IN PATIENTS WITH FAMILIAL EXUDATIVE VITREORETINOPATHY AND CONTROL SUBJECTS

AGGREGATION INDUCER AND CONCENTRATION	PATIENTS			CONTROL SUBJECTS		
	NO.	UNITS OF AGGREGATION		NO.	UNITS OF AGGREGATION	
		MEAN	S.D.		MEAN	S.D.
Adenosine diphosphate 10^{-6} mol/l	7	117	26	10	130	14
Adenosine diphosphate 4×10^{-7} mol/l	4	111	17	10	119	26
Adenosine diphosphate 2×10^{-7} mol/l	6	99	15	9	94	28
Collagen 2×10^{-5} l	7	98	17	10	115	11
Collagen 5×10^{-6} l	6	92	7	7	96	14
Arachidonic acid 5 mmol/l	7	76	5	8	65	6
Arachidonic acid 1.5 mmol/l	7	23	4	10	17	11

Mann[27] postulated that a falciform retinal fold resulted from local accretion between the primary vitreous and the inside of the optic cup. Michaelson[28] and Pruett[29] maintained that the anomaly resulted from persistent hyperplastic primary vitreous in the posterior part of the vitreous space. These theories concerning the primary vitreous are no longer tenable because falciform folds develop as a complication of familial exudative vitreoretinopathy, a disease not associated with disorders of the primary vitreous development. I believe the falciform fold that develops in familial exudative vitreoretinopathy has a pathogenesis similar to that of the fold, which may develop in retinopathy of prematurity.

Chaudhuri and associates[10] reported disturbed platelet aggregation, especially after induction with a low concentration of arachidonic acid (1.5 mmol/l). They speculated that a deficiency of thromboxane A_2 (a potent vasoconstrictor) might play a role in the pathogenesis of the vascular anomalies in familial exudative vitreoretinopathy. This prompted me to repeat platelet aggregation tests in patients with familial exudative vitreoretinopathy, using the same inducers and identical concentrations. I was unable to demonstrate any significant difference in platelet aggregation be-

tween patients and control subjects. These results agree with those reported by Friedrich, Francis, and Kim.[30] However, they found an increased bleeding time in one patient with familial exudative vitreoretinopathy. My hematologic findings do not indicate an abnormal bleeding time in this disorder.

The presence and growth of nonfibrotic neovascularizations were observed in some of the patients older than six years of age; in retinopathy of prematurity this has rarely been described. The clinical features of the two diseases are therefore not always identical.

Vitreous hemorrhage can be a serious complication at a young age, as I have observed in a few infants. In one untreated eye, the hemorrhage was followed by a total retinal detachment with a closed funnel within a few weeks. These observations warrant regular examinations of the peripheral fundi of young children and prompt cryocoagulation or laser coagulation of any new vessels. Small neovascularizations generally showed rapid regression after therapy (Fig. 8).

Adult eyes sometimes showed small, partly fibrotic new vessels that were asymptomatic and did not change during years of observation. In such patients, periodic checkups would seem to be sufficient.

Retinal detachment in familial exudative vitreoretinopathy shows numerous clinical variations and usually occurs at an early age. In my patients, all detachments had occurred before age 30 years, with the exception of one rhegmatogenous detachment seen in a 56-year-old man.

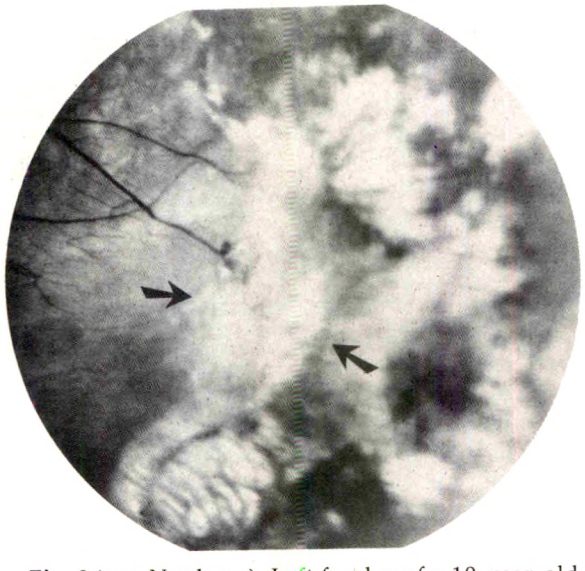


Fig. 8 (van Nouhuys). Left fundus of a 10-year-old girl. Fibrotic tissue (arrows) as a remnant of neovascularization two years after cryocoagulation of the peripheral retina.

Traction on the peripheral retina seems to be the principal cause of retinal detachment in familial exudative vitreoretinopathy. In some cases, this traction displaces the retina without visible breaks. The best example of a tractional detachment is the frequently observed falciform retinal fold. Often, however, traction causes retinal defects, which may vary widely in size and shape (Fig. 6).

Retinal detachment in familial exudative vitreoretinopathy proved to be a serious complication with a relatively unfavorable course. Of 41 eyes (37 eyes of patients with familial exudative vitreoretinopathy and four eyes of patients with sporadic exudative vitreoretinopathy), 22 with retinal detachment had not been treated with retinal surgery. Generally, this was because of the poor prognosis concerning visual improvement, especially in patients with falciform retinal folds or chronic detachments associated with severe proliferative vitreoretinopathy.

Retinal surgery in familial exudative vitreoretinopathy was often complicated by nonattachment or redetachment after surgery. In only seven eyes the retina was reattached after one or more operations. Complications after operative therapy have been previously reported.[7,31] The results of retinal surgery seemed to be related to the age of the patients at the time of operation. All operations on eyes of patients younger than the age of 19 years were unsuccessful, whereas the retinas of all eyes of patients older than 19 years of age were treated successfully. In the eyes of patients older than 19 years of age, extensive proliferative vitreoretinopathy was an unusual feature, whereas the retinal detachments in the younger patients were more prone to develop this complication, often before surgery. Therefore, pars plana vitrectomy was the main surgical procedure in the younger patients, whereas a scleral buckling technique was performed in most of the older patients. In children with familial exudative vitreoretinopathy and retinal detachment, the surgeon faces the same problems as in the treatment of retinal detachment in patients with retinopathy of prematurity. In patients with retinopathy of prematurity, also in the older patients with regressed retinopathy of prematurity, the risk of recurrent retinal detachment is greater than normal.[32]

Virtually all patients with familial exudative vitreoretinopathy showed a pedigree consistent

with autosomal dominant transmission of the gene. Five patients, including identical twins, had no close relatives with perceptible anomalies. Such solitary cases of patients with ocular anomalies identical to those of familial exudative vitreoretinopathy have also been observed by other investigators.[12] Whether such cases involve a mutation, nonpenetrance of the autosomal dominant gene in one of the parents, or genetic heterogeneity is unknown.

ACKNOWLEDGMENT

The hematologic studies were performed at the Department of Hematology, University of Nijmegen, The Netherlands.

References

1. Criswick, V. G., and Schepens, C. L.: Familial exudative vitreoretinopathy. Am. J. Ophthalmol. 68:578, 1969.

2. Gow, J., and Oliver, G. L.: Familial exudative vitreoretinopathy. Arch. Ophthalmol. 86:150, 1971.

3. Canny, C. L. B., and Oliver, G. L.: Fluorescein angiographic findings in familial exudative vitreoretinopathy. Arch. Ophthalmol. 94:1114, 1976.

4. Slusher, M. M., and Hutton, W. E.: Familial exudative vitreoretinopathy. Am. J. Ophthalmol. 87:152, 1979.

5. Ober, R. R., Bird, A. C., Hamilton, A. M., and Sehmi, K.: Autosomal dominant exudative vitreoretinopathy. Br. J. Ophthalmol. 64:112, 1980.

6. Nijhuis, F. A., Deutman, A. F., and Aan de Kerk, A. L.: Fluorescein angiography in mild stages of dominant exudative vitreoretinopathy. Mod. Probl. Ophthalmol. 20:107, 1979.

7. Laqua, H.: Familial exudative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 213:121, 1980.

8. van Nouhuys, C. E.: Dominant exudative vitreoretinopathy and other vascular developmental disorders of the peripheral retina. Doc. Ophthalmol. 54:1, 1982.

9. Goldschmidt, R.: Gen und Ausseneigenschaft. Z. Vererbungslehre 69:38, 1935.

10. Chaudhuri, P. R., Rosenthal, A. R., Goulstine, D. B., Rowlands, D., and Mitchel, V. E.: Familial exudative vitreoretinopathy associated with familial thrombocytopathy. Br. J. Ophthalmol. 67:755, 1983.

11. Imandt, L., Genders, T., Wessels, J., and Haanen, C.: An improved method for preparing platelet-rich plasma. Thromb. Res. 11:429, 1977.

12. Miyakubo, H., Inohara, N., and Hashimoto, K.: Retinal involvement in familial exudative vitreoretinopathy. Ophthalmologica 185:125, 1982.

13. Miyakubo, H., Hashimoto, K., and Miyakubo, S.: Retinal vascular pattern in familial exudative vitreoretinopathy. Ophthalmology 91:1524, 1984.

14. Tasman, W., Augsburger, J., Shields, J. A., Caputo, A., and Annesley, W. H.: Familial exudative vitreoretinopathy. Trans. Am. Soc. Ophthalmol. 74:211, 1981.

15. Brockhurst, R. J., Albert, D. M., and Zakov, Z. N.: Pathological findings in familial exudative vitreoretinopathy. Arch. Ophthalmol. 99:2143, 1981.

16. Boldrey, E. E., Egbert, P., Gass, J. D. M., and Friberg, T.: The histopathology of familial exudative vitreoretinopathy. Arch. Ophthalmol. 103:238, 1985.

17. Nicholson, D. H., and Galvis, V.: Criswick-Schepens syndrome (familial exudative vitreoretinopathy). Study of a Colombian kindred. Arch. Ophthalmol. 102:1519, 1984.

18. van Nouhuys, C. E.: Juvenile retinal detachment as a complication of familial exudative vitreoretinopathy. Fortschr. Ophthalmol. 86:221, 1989.

19. Schulman, J., and Merin, S.: Hereditary vitreoretinal degenerations. In Newsome, D. A. (ed.): Retinal Dystrophies and Degenerations. New York, Raven Press, 1988, pp. 95.

20. Machemer, R.: Description and pathogenesis of late stages of retinopathy of prematurity. Ophthalmology 92:1000, 1985.

21. Feldman, E. L., Norris, J. L., and Cleasby, G. W.: Autosomal dominant exudative vitreoretinopathy. Arch. Ophthalmol. 101:1532, 1983.

22. Foos, R. Y., and Kopelow, S.: Development of retinal vasculature in perinatal infants. Surv. Ophthalmol. 18:117, 1973.

23. Dudgeon, J.: Familial exudative vitreoretinopathy. Trans. Ophthalmol. Soc. U.K. 99:45, 1979.

24. van Nouhuys, C. E.: Congenital retinal fold as a sign of dominant exudative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 217:55, 1981.

25. Nishimura, M., Yamana, T., Sugino, M., Kohno, T., Yamana, Y., Minei, M., and Sanui, H.: Falciform retinal fold as a sign of familial exudative vitreoretinopathy. Jpn. J. Ophthalmol. 27:40, 1983.

26. Spallone, A.: Differential diagnosis of hereditary vitreoretinopathy. Milan, Italy, Fogliazza Editore, 1989, pp. 23–30.

27. Mann, I.: Congenital retinal fold. Br. J. Ophthalmol. 19:641, 1935.

28. Michaelson, I. C.: Intertissue vascular relationships in the fundus of the eye. Invest. Ophthalmol. 5:1004, 1965.

29. Pruett, R. C.: The pleomorphism and complications of posterior hyperplastic primary vitreous. Am. J. Ophthalmol. 80:625, 1975.

30. Friedrich, C. A., Francis, K. A., and Kim, H. C.: Familial exudative vitreoretinopathy (FEVR) and platelet dysfunction. Br. J. Ophthalmol. 73:477, 1989.

31. Okubo, Y., Okubo, A., Kubono, T., and Shimizu, H.: Familial exudative vitreoretinopathy, rhegmatogenous retinal detachment and postoperative uveitis with massive subretinal exudation. Acta Soc. Ophthalmol. Jpn. 88:1151, 1984.

32. Sneed, S. R., Pulido, J. S., Blodi, C. F., Clarkson, J. G., Flynn, H. W., Jr., and Mieler, W. F.: Surgical management of late-onset retinal detachments associated with regressed retinopathy of prematurity. Ophthalmology 97:179, 1990.

Photic Retinal Injury From Endoillumination During Vitrectomy

Ferenc Kuhn, M.D., Robert Morris, M.D., and Michael Massey, M.D.

We treated a patient who developed a paramacular area of light-induced retinal damage after endoscopic epimacular membrane removal. Postoperative color photographs showed complete absence of the membrane, but fluorescein angiography demonstrated a previously absent superior paramacular lesion consistent with a photic injury. Operative microscope illumination had been eliminated by corneal shielding, which implicated endoillumination as the source of injury. We recommend the following procedures to avoid this complication: careful planning of vitreous surgery for epimacular membrane removal; using filters; minimizing the length of surgery; keeping the light output low; maintaining maximal light pipe distance from the retina; eccentric orientation of the light pipe; and use of intermittent and variable site illumination techniques.

THE POSSIBILITY that the operating microscope may cause photic retinal damage was suggested in 1977[1] and confirmed in 1983.[2,3] Reports of this occurrence have since proliferated.[4-8] Experimental data and clinical observations have indicated that light-induced retinal injury may also be a complication of the application of the indirect ophthalmoscope,[9-11] the slit lamp, and the overhead surgical lamp.[12] Several experimental studies have demonstrated the potential for retinal photic toxicity caused by endoillumination.[13-15] McDonald, Verre, and Aaberg[16] described lesions similar to retinal light burns produced by the operating microscope, which they believed to be caused by an endoilluminator. We treated a patient who developed photic retinal injury associated only with fiberoptic endoillumination.

Accepted for publication Sept. 4, 1990.

From the Helen Keller Eye Research Foundation, and the Eye Foundation Hospital/University of Alabama Combined Program in Ophthalmology, Birmingham, Alabama. Dr. Kuhn is a Rich Retina Research Fellow.

Reprint requests to Robert Morris, M.D., Helen Keller Eye Research Foundation, 700 S. 18th St., Birmingham, AL 35233.

Case Report

An 85-year-old woman had sudden visual deterioration in the right eye. Five years previously, the patient had had cataract surgery with posterior chamber intraocular lens implantation, recovering 20/20 visual acuity postoperatively. On admission, she had visual acuity of hand motions in the right eye because of dense vitreous hemorrhage and a retinal detachment that involved the macula. Visual acuity was 20/20 in the left eye.

The patient underwent a trans pars plana vitrectomy with endodrainage of subretinal fluid, air-fluid exchange, exocryopexy of a horseshoe retinal tear, and implantation of an encircling band. One month later, visual acuity improved to 20/400 with complete retinal reattachment. Visual acuity three months postoperatively reached 20/160, but a dense epimacular proliferation caused significant prefoveal opacity and distortion (Figure, top left and top right).

The epimacular membrane was removed five months after retinal detachment surgery. According to the hospital operative record, a "very thick, and somewhat friable, not completely mature membrane was peeled off with great patience." Less than two months later, visual acuity had improved to 20/80, and no residual membrane could be detected. An oval area of 1 disk diameter was observed to have faint depigmentation 1 disk diameter superior to the fovea (Figure, bottom left). Fluorescein angiography showed hyperfluorescence with mottled hypofluorescence over the corresponding area (Figure, bottom right).

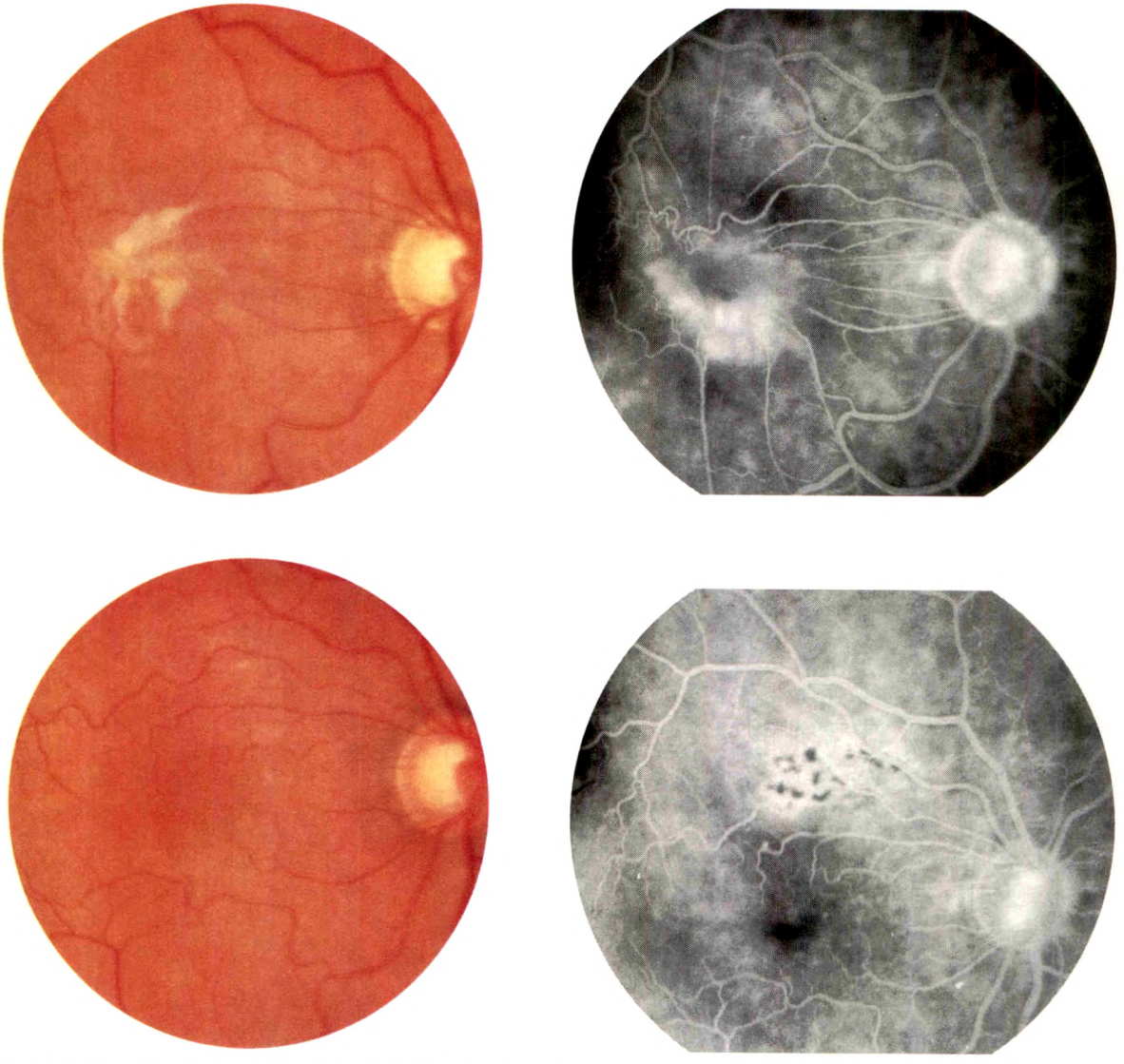


Figure (Kuhn, Morris, and Massey). Top left, Preoperative appearance of epimacular membrane with severe distortion and prefoveal opacity. Note healthy retina superior to the fovea. Top right, Preoperative fluorescein angiogram showing severely distorted vessels but normal area superior to the macula. Bottom left, Two months postoperatively, the epimacular membrane is absent but discrete depigmentation is visible superior to the fovea. Bottom right, Postoperative fluorescein configuration showing an oval lesion of hyperfluorescence with mottled hypofluorescence, consistent with photic injury, in the corresponding area.

Discussion

Several extraocular light sources are known to cause potential retinal injury. Solar observation may result in foveomacular retinitis.[17] A similar clinical course can be seen in patients with welding arc exposure.[18] Retinal damage may also occur because of radiant energy,[19] atomic bomb explosion,[20] and industrial lasers.[21] Although chorioretinal burn is a goal of retinal laser surgery, it is a hazard associated with many other ophthalmic devices.[1-3,8-12,16,22-24] In one study, maculopathy induced by the operating microscope was detected in no less than 7% of patients undergoing cataract surgery.[25]

The eye has several protective mechanisms against damage caused by light. The globe is

partially shadowed by the eyebrow ridge. If light is excessive, the eye turns away from the light source, the cornea can rapidly be covered by the eyelids, or the palpebral fissure is narrowed (squint).[26,27] The cornea reflects most light not perpendicular to its surface (according to Fresnel's law, 30% to 60% of all overhead radiation is so reflected) and is opaque to ultraviolet light below 300 nm.[26] The pupillary constriction reflex reduces retinal irradiance by the square of the power level.[28] The crystalline lens filters out most radiation in the near-ultraviolet spectrum between 300 and 400 nm.[29] The retina itself has additional protective measures against injury caused by light. Xanthophyll reduces photoreceptor exposure to near-ultraviolet and blue light[30]; photoreceptor exposure to light scattered back from the retinal pigment epithelium and choroid is reduced by melanin; and melanin also protects against toxic-free radicals and toxic chemicals.[31]

With the exception of retinal sources of protection, however, none of these mechanisms are available for the individual exposed to a light source introduced into the eye, such as in vitreous surgery. In an animal model, light-induced retinal damage was observed from a stationary fiberoptic endoilluminator at 2 mm from the retina. Using a 150-W halogenated tungsten projector bulb, ten minutes of exposure was enough to cause histologic changes in the outer retina; 15 minutes of exposure resulted in ophthalmoscopically visible retinal damage.[13]

The danger of iatrogenic endoscopic photic injury with subsequent visual impairment is greatest when vitrectomy is performed for the removal of an epimacular membrane. The surgeon is often forced to keep a fiberoptic tip over the same small retinal area for a considerable time. Photic retinal injury not attributed to the operating microscope has been reported in one patient who developed two areas of retinal burn presumed secondary to fiberoptic endoillumination.[16] It seems probable, however, that the actual number of such injuries is higher but that they are overlooked or unreported. A contributory factor, perhaps, is that photic injuries are less evident on ophthalmoscopy than on fluorescein angiography (Figure, bottom left and bottom right).

The possibility of photic retinal injury associated with endoscopic epimacular membrane removal requires the surgeon to undertake maximal protective measures. The most harmful ultraviolet and near-ultraviolet portions of the spectrum are almost entirely eliminated from the intraocular light source by using filters. One study found that only 3% of the light provided by an intraocular fiberoptic cable was below 500 nm.[14] Filters, however, are not the ultimate solution. In a human experiment, both ends of the visible spectrum were blocked by filters so that transmittance was less than 5% both at wavelengths greater than 750 nm and shorter than 420 nm. Nevertheless, one-hour exposure to a 150-W tungsten-halogen bulb of the operating microscope caused photic retinopathy.[8]

Reducing the power of illumination is a logical solution. Robertson and McLaren,[8] however, found that a typical photic retinal lesion was produced despite reduction by one fourth of the overall light energy. If video recording of surgery is required, it may be difficult to find the appropriate compromise between "still sufficient" and "not harmful" amounts of light.

Keeping the fiberoptic light pipe as far as possible from the retinal surface is another useful suggestion. In the study of Meyers and Bonner,[14] the threshold to retinal damage in the owl monkey was almost tenfold higher with the fiberoptic at 6 mm from the retina as compared to only 2 mm from the retina. In some clinical situations, however, the surgeon cannot avoid using the light probe in close proximity to the retina. For example, bimanual manipulations are sometimes necessary, and the light probe frequently acts as a second instrument. The pic light probe was specifically designed for this purpose.

Although retinal damage still occurs if light exposure is intermittent, it is less severe as compared to the same amount of light administered continuously.[32] This logical experimental conclusion, however, has not been replicated with human subjects.

A possible preventive method involves reducing the temperature of the vitreous compartment and, presumably, the retina. Rinkoff and associates[15] cooled the vitrectomy infusion fluid from body temperature to room temperature, which extended the damage threshold from 25 to 60 minutes. Another well-designed study, however, demonstrated retinal phototoxicity after as little as five minutes of close endoillumination, independent of infusion fluid temperature (unpublished data).

In reviewing our case, no doubt exists as to the source of photic injury. A corneal opaque shield was used during all operative micro-

scope illumination. Additionally, the patient's operative hospital record stated that to remove the friable and immature membrane completely, great patience was necessary; that is, the light source must have been kept over the same retinal spot for a prolonged period, and peeling was initiated from the corresponding superior location. Finally, it is the operative habit of one of us (R.M.) to place the endoilluminator in this paramacular location during prolonged epimacular membrane removal procedures to protect the fovea.

Our recommendations to avoid photic retinal injury from the endoilluminator include the following: be aware of possible photic retinal injury when preparing surgical strategy; make use of available filters; attempt to minimize the length of surgery; use minimal necessary light output; maintain maximal light pipe distance from the retinal surface consistent with safe membrane manipulation; even for the removal of a foveal membrane, maintain an eccentric orientation of the light pipe; avoid prolonged, continuous stationary positioning of the fiberoptic probe, even when close work is required; and if prolonged manipulation at a single site is necessary, use an intermittent light exposure.

References

1. Henry, M. M., Henry, L. M., and Henry, L. M.: A possible cause of chronic cystic maculopathy. Ann. Ophthalmol. 9:455, 1977.
2. Macy, J. I., and Baerveldt, G.: Pseudophakic serous maculopathy. Arch. Ophthalmol. 101:228, 1983.
3. McDonald, H. R., and Irvine, A. R.: Light-induced maculopathy from the operating microscope in extracapsular cataract extraction and intraocular lens implantation. Ophthalmology 90:945, 1983.
4. Robertson, D. M., and Feldman, R. B.: Photic retinopathy from the operating room microscope. Am. J. Ophthalmol. 101:561, 1986.
5. Irvine, A. R., Wood, I., and Morris, B. W.: Retinal damage from the illumination of the operating microscope. An experimental study in pseudophakic monkeys. Arch. Ophthalmol. 102:1358, 1984.
6. Jampol, L. M., Kraff, M. C., Sanders, D. R., Kenneth, A., and Lieberman, H.: Near-UV radiation from the operating microscope and pseudophakic cystoid macular edema. Arch. Ophthalmol. 103:28, 1985.
7. Feldman, R. B., and Robertson, D. R.: Photic retinopathy from the operating microscope. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1986, p. 19.
8. Robertson, D. M., and McLaren, J. W.: Photic retinopathy from the operating microscope. Study with filters. Arch. Ophthalmol. 107:373, 1989.
9. Friedman, E., and Kuwabara, T.: The retinal pigment epithelium. IV. The damaging effects of radiant energy. Arch. Ophthalmol. 80:265, 1968.
10. Ts'o, M. O. M., Fine, B. S., and Zimmerman, L. E.: Photic maculopathy produced by the indirect ophthalmoscope. I. Clinical and histopathologic study. Am. J. Ophthalmol. 73:686, 1972.
11. Robertson, D. M., and Erickson, G. J.: The effect of prolonged indirect ophthalmoscopy of the human eye. Am. J. Ophthalmol. 87:652, 1979.
12. Calkins, J. L., and Hochheimer, B. F.: Retinal light exposure from ophthalmoscopes, slit lamps, and overhead surgical lamps. Invest. Ophthalmol. Vis. Sci. 19:1009, 1980.
13. Fuller, D., Machemer, R., and Knighton, R. W.: Retinal damage produced by intraocular fiber optic light. Am. J. Ophthalmol. 85:519, 1978.
14. Meyers, S. M., and Bonner, R. F.: Retinal irradiance from vitrectomy endoilluminators. Am. J. Ophthalmol. 94:26, 1982.
15. Rinkoff, J., Machemer, R., Hida, T., and Chandler, D.: Temperature-dependent light damage to the retina. Am. J. Ophthalmol. 102:452, 1986.
16. McDonald, H. R., Verre, W. P., and Aaberg, T. M.: Surgical management of idiopathic epiretinal membranes. Ophthalmology 93:978, 1986.
17. Cordes, F. C.: A type of foveo-macular retinitis observed in the U.S. Navy. Am. J. Ophthalmol. 27:803, 1944.
18. Naidoff, M. A., and Sliney, D. H.: Retinal injury from a welding arc. Am. J. Ophthalmol. 77:663, 1974.
19. Verhoeff, F. H., and Bell, L.: The pathological effects of radiant energy on the eye. Proc. Am. Acad. Arts Sci. 51:629, 1916.
20. Buettner, K., and Rose, H. W.: Eye hazards from atomic bomb light. Sight Sav. Rev. 23:1, 1953.
21. Rathkey, A. S.: Accidental laser burn of the macula. Arch. Ophthalmol. 74:346, 1965.
22. Boldrey, E. E., Ho, B. T., and Griffith, R. D.: Retinal burns occurring at cataract extraction. Ophthalmology 91:1297, 1984.
23. Brod, R. D., Barron, B. A., Suelflow, J. A., Franklin, R. M., and Packer, A. J.: Phototoxic retinal damage during refractive surgery. Am. J. Ophthalmol. 102:121, 1986.
24. Khwarg, S. G., Geoghegan, M., and Hanscom, T. A.: Light-induced maculopathy from the operating microscope. Am. J. Ophthalmol. 98:628, 1984.
25. Khwarg, S. G., Linstone, F. A., Daniels, S. A., Isenberg, S. J., Hanscom, T. A., Geoghegan, M., and Straatsma, B. R.: Incidence, risk factors, and morphology in operating microscope light retinopathy. Am. J. Ophthalmol. 103:255, 1987.

26. Sliney, D. H.: Eye protective techniques for bright light. Ophthalmology 90:937, 1983.
27. Mainster, M. A.: Photic retinal injury. In Ryan, S. J. (ed.): Retina, vol. 2. St. Louis, C. V. Mosby, 1989, p. 749.
28. Michels, M., and Sternberg, P., Jr.: Operating microscope–induced retinal phototoxicity. Pathophysiology, clinical manifestations and prevention. Surv. Ophthalmol. 34:237, 1990.
29. Boettner, E. A., and Wolter, J. R.: Transmission of the ocular media. Invest. Ophthalmol. Vis. Sci. 1:776, 1962.
30. Kirschfeld, K.: Carotenoid pigments. Their possible role in protecting against photooxidation in eyes and photoreceptor cells. Proc. R. Soc. Lond. [Biol.] 216:71, 1982.
31. Ham, W. T., Mueller, H. A., Ruffolo, J. J., Jr., Millen, J. E., Cleary, S. F., Guerry, R. K., and Guerry, D., III: Basic mechanisms underlying the production of photochemical lesions in the mammalian retina. Curr. Eye Res. 3:165, 1984.
32. Lee, F. L., Yu, D. Y., and Ts'o, M. O. M.: Effect of continuous versus multiple intermittent light exposures on rat retina. Curr. Eye Res. 9:11, 1990.

OPHTHALMIC MINIATURE

The walls were pale blue, and an assortment of framed Broadway posters hung from them, old broadsides advertising *Oklahoma!*, *Mame*, *The Sound of Music*. Aside from them, there was only one other picture, a very ornately drawn portrait of a woman whose eyes seemed to watch the world from behind a pale, gossamer screen. The eyes themselves were large and blue, and something about them disturbed him. For a time, he couldn't quite figure out what it was. Then, suddenly, he knew. Their color was the exact shade of the walls. Frank realized that either the walls or the eyes had been painted to match the other's color.

Thomas Cook, *Night Secrets*
New York, G. P. Putnam's Sons, p. 96

Light Damage in Detached Retina

John D. Zilis, M.D., and Robert Machemer, M.D.

We injected homologous fibroblasts over the retinal vascular wing in five rabbits to induce a tractional retinal detachment. Eleven days later, a focal area of detachment was exposed to 30 minutes of visible light by an intraocular fiberoptic probe. Histologic damage to the detached retina exposed to light was demonstrated. The outer retina was affected most severely.

LIGHT DAMAGE IN ATTACHED RETINA has been demonstrated with various ophthalmic light sources, including the intraocular fiberoptic probe.[1,2] This damage primarily involves the outer retina and pigment epithelium,[2-5] but it can also affect the inner retina if exposure is intense and of long duration.[6] The exact mechanisms of such retinal damage and the role of the melanin-containing retinal pigment epithelium[7-9] remain unknown. We evaluated light damage in experimentally detached rabbit retina that had been separated from the retinal pigment epithelium.

Material and Methods

Five pigmented rabbits weighing between 2.5 and 3.5 kg were housed under 50 foot-candle (ft-c) illumination on a 12-hour, light-dark cycle. At least two weeks before the experiments, the rabbits were given anesthesia with an intramuscular injection of ketamine hydrochloride (30 mg/kg of body weight) and xylazine hydrochloride (5 mg/kg of body weight). Pupils were dilated by a 1:1 mixture of 0.25% tropicamide and 5% phenylephrine hydrochloride. The peripheral retina was treated for 360 degrees at a distance of 4.5 mm from the corneoscleral limbus with transscleral cryopexy, under direct visual observation, in preparation for future sclerotomy sites.

At least two weeks later, the vitreous cavities were injected with 250,000 homologous tissue-cultured fibroblasts. Fibroblasts were of a single line and had been harvested from rabbit rump dermis and tissue cultured in Dulbeccos modified Eagle medium with 10% fetal bovine serum, antibiotics, and antimycotics, and maintained at 37 C in an incubator with an atmosphere of 5% carbon dioxide in air. These were harvested for injection in a manner previously described.[10]

At the time of injection, the animals were again given anesthesia, and the pupils were dilated. Under direct visualization by the indirect ophthalmoscope, the cells, suspended in 0.1 ml of phosphate-buffered saline, were injected slowly through the previously cryotreated peripheral retina into the vitreous body over the vascular wing of the retina. The animals were placed on their sides for one hour to allow settling of cells to occur on the vascularized retina. Indirect ophthalmoscopy was performed at Day 1 and Day 7 after injection to monitor progression of the proliferative response and resulting tractional retinal detachment.

Eleven days after fibroblast injection, the animals were again given anesthesia, and the pupils of the injected eyes were dilated. Retrobulbar injections were not given. Rectal temperatures were monitored, and warming blankets were used to maintain body temperature as needed.

Sclerotomies were made 3.0 mm posterior to the corneoscleral limbus through previously cryotreated peripheral retina, and cannulas were placed to maintain an opening. Two additional sclerotomies were placed for infusion and outflow. Midvitreous temperature was ob-

Accepted for publication Sept. 12, 1990.

From the Devers Eye Institute, Portland, Oregon (Dr. Zilis), and Department of Ophthalmology, Duke University, Durham, North Carolina (Dr. Machemer). This study was supported by National Eye Institute grant F32 EY06046-01, the Helena Rubinstein Foundation, New York, New York, and Research to Prevent Blindness, Inc.

Reprint requests to Robert Machemer, M.D., Duke University Eye Center, Box 3802, Durham, NC 27710.

tained before beginning infusion and monitored during infusion by a temperature probe. Lactated Ringer's infusion fluid was warmed to 39.5 ± 0.5 C in a water bath that was elevated 26 inches above the level of the eye. Intraocular pressure was maintained between 14 and 21 mm Hg, and intraocular temperature was maintained at 38.3 ± 0.3 C by constant perfusion of lactated Ringer's solution.

A glass fiberoptic probe attached to a light source with a 150-W, 21-V tungsten-halogen projector bulb had a measured light output of 40.0 ± 0.8 ft-c. To confirm constant light output, the light measurement was performed before and after the experiment by a radiometer/photometer with integrating sphere.

The sclerotomy created for introduction of the fiberoptic probe was made inferiorly. The probe was advanced slowly by a micromanipulator to a distance of 1.0 mm from the detached retina, which created an approximate circle of light measuring 2.0 mm in its widest diameter as measured by the ocular micrometer of the surgical microscope. The area of the smoothly detached retina exposed to light was centered 1.5 mm below the edge of the myelinated nerve layer and 1 disk diameter temporal to the disk in avascular retina. The calculated retinal irradiance was 0.34 W/cm^2, which correlated well with previous in vitro measurements made by a similar experimental set-up.[4] Light exposure was maintained for 30 minutes. The position of the fiberoptic probe was checked frequently during the procedure.

After 30 minutes, the instruments and cannulas were removed and the sclerotomies were closed with 7-0 Vicryl sutures. The conjunctivae were closed, and 5 mg of gentamicin sulfate was injected subconjunctivally. Atropine 1% ointment was placed on the corneas.

Postoperatively, the animals were examined daily by the indirect ophthalmoscope. On the third postoperative day, the animals were killed, and the eyes were injected with 3% glutaraldehyde in 0.1 mol/l of cacodylate buffer immediately before enucleation. Additional glutaraldehyde was injected through 3.0-mm radial incisions bisecting the inferior corneoscleral limbus, and the eyes were refrigerated and fixed for 48 hours.

Posterior eye cups were prepared, and 3.0 × 3.0-mm sections of retina centered in the area of light exposure were removed. Adjacent 3.0 × 3.0-mm areas of detached retina were also sectioned and examined.

The specimens were processed in 2% buffered osmium tetroxide through graded alcohol and embedded in epoxy resin plastic. Sections were stained with methylene blue and azure II for light microscopy, and thin sections were prepared and stained with uranyl acetate and lead citrate for transmission electron microscopy.

Results

Tractional retinal detachments developed within seven days of the fibroblast injection in all rabbits. The detachment was highest in the area of the vascular medullary wing from which a proliferative fibroblast strand extended to the area of the injection site (Fig. 1). The avascular retina below the wing was elevated with a defined inferior demarcation line separating the remaining attached retina from the gray-white detached retina. Subretinal white precipitates were sometimes noted in the dependent portion of the detachment. Rabbits that developed rhegmatogenous, bullous detachments were excluded.

A total of five pigmented rabbits fulfilled the experimental criteria. Daily postoperative indirect ophthalmoscopic examinations were performed. On the first postoperative day, all eyes displayed significant posterior intraocular in-

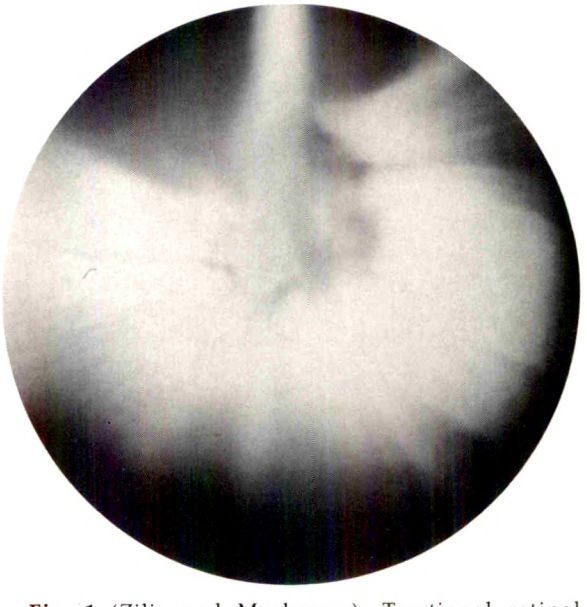


Fig. 1 (Zilis and Machemer). Tractional retinal detachment of vascular medullary wings in a rabbit. Note proliferative fibroblast strand superiorly.

flammation that obscured retinal detail. Progressive clearing, however, occurred by Day 3, which allowed observation of the area of light exposure. Focal retinal edema was not found, although slight retinal thinning was suspected in two animals.

Histologically, the eyes of all five animals had much more severe damage in the area of light exposure than in other areas of retinal detachment. In the area of retinal detachment not exposed to light, patchy loss of photoreceptor outer segments and occasional macrophage infiltration were noted. Generally, cellular organization of retinal layers was well maintained (Fig. 2).

Conversely, the areas of detached retina exposed to light displayed extreme destruction (Fig. 3). The photoreceptor elements were virtually eliminated with only small degenerated inner segments remaining. Macrophages were found along the outer limiting membrane. The outer nuclear layer demonstrated nuclear dropout and pyknosis. The inner retinal layers were relatively well preserved, although small cystic spaces were observed.

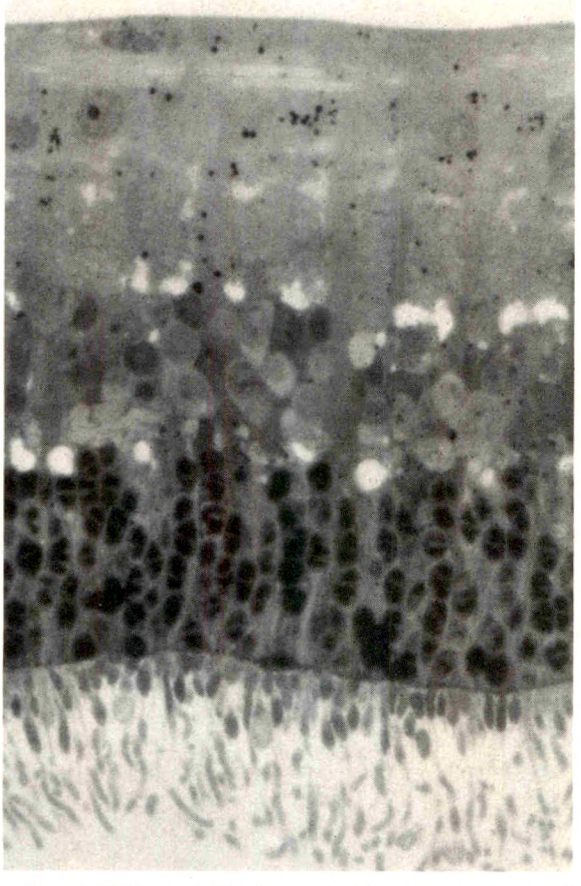


Fig. 2 (Zilis and Machemer). Photomicrograph of detached retina without light exposure (× 400).

Discussion

Retinal damage caused by visible light is known to occur when an intraocular fiberoptic light source is used.[2,4] In attached retina, histologic damage has been demonstrated primarily in the outer retina and pigment epithelium.[2-5] Noell and associates[3] speculated that the damage is caused by photochemical events that are sensitive to changes in temperature.

The melanin-containing retinal pigment epithelium demonstrated damage when exposed to visible light, although its role in mediating

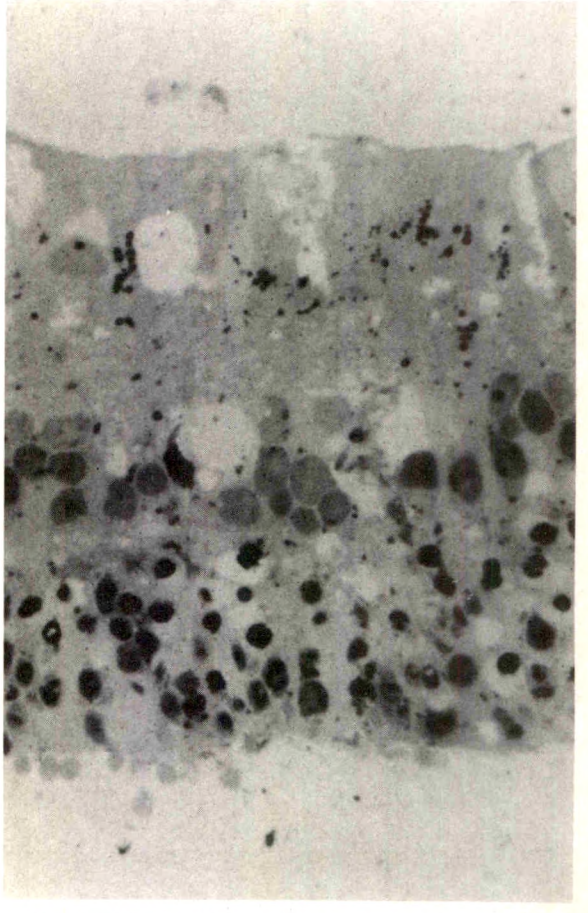


Fig. 3 (Zilis and Machemer). Photomicrograph of detached retina with 30 minutes of light exposure. Note massive destruction of outer retina and loss of photoreceptors (× 400).

damage to the overlying retina remains unknown. Ham and associates[11] originally suggested that the site of injury in the rhesus monkey may be the melanin granules of the melanosomes of the retinal pigment epithelium. During the first 48 hours after light exposure, damage appeared confined to this layer, whereas overlying photoreceptor outer segments remained intact.

Working with the rat, however, Rapp and Williams[8] showed almost equal retinal sensitivity to light damage in both pigmented and albino animals. Hoeppler and associates[9] found essentially no difference when morphologic damage was compared in pigmented and albino rabbits, which led them to postulate that melanin may not be critically involved in light damage to the retina.

We designed this study to assess light damage in retina that was detached from the retinal pigment epithelium. To maximize light damage, a relatively long exposure (30 minutes) of visible light was placed on a small area (2.0-mm diameter) of detached, avascular rabbit retina at body temperature. This resulted in severe histologic damage to the retina (Fig. 3), which was much more profound than the usual outer retinal degeneration expected in detached retina.[12,13] Indeed, the damage was dramatic when compared to adjacent areas of detached retina not exposed to the fiberoptic light (Fig. 2).

In the light-exposed detached retina, damage was most apparent in the outer retina with resulting destruction of photoreceptor inner and outer segments and their nuclei. The same pattern of damage was noted in light exposure to attached retina.[4,9] In attached retina, the outer retina is extremely active, metabolically, and well oxygenated from the underlying choroid. Because of this, one proposed mechanism of light damage to the retina involves photooxidative and photodynamic reactions involving the retinal pigment epithelium with generation of destructive oxygen-derived free radicals.[14] Because we found a similar pattern of damage in the outer detached retina that was devoid of melanin and presumed to be ischemic, additional undefined mechanisms or mediators may play a role. We also conclude from our experiments that light damage in detached retina may occur with light sources commonly used by clinicians, particularly during lengthy vitreoretinal surgical procedures.

References

1. Calkins, J. L., Hochheimer, B. F., and D'Anna, S. A.: Potential hazards from specific ophthalmic devices. Vision Res. 20:1039, 1980.

2. Fuller, D., Machemer, R., and Knighton, R. W.: Retinal damage produced by the intraocular fiber optic light. Am. J. Ophthalmol. 85:519, 1978.

3. Noell, W., Walker, V. S., Kang, B. S., and Bergman, S.: Retinal damage by light in rats. Invest. Ophthalmol. Vis. Sci. 5:450, 1966.

4. Rinkoff, J., Machemer, R., Hida, T., and Chandler, D.: Temperature-dependent light damage to the retina. Am. J. Ophthalmol. 102:452, 1986.

5. T'so, M. O. M., Fine, B. S., and Zimmerman, L. E.: Photic maculopathy produced by the indirect ophthalmoscope. I. Clinical and histopathologic study. Am. J. Ophthalmol. 73:686, 1972.

6. Lawwill, T.: Three major pathologic processes caused by light in the primate retina. A search for mechanisms. Trans. Am. Ophthalmol. Soc. 80:516, 1982.

7. Ham, W. T., Ruffolo, J. J., and Mueller, H. A.: The nature of retinal radiation damage. Dependence on wave length, power level and exposure time. Vision Res. 20:1105, 1980.

8. Rapp, L. M., and Williams, T. P.: The role of ocular pigmentation in protecting against retinal light damage. Vision Res. 20:1127, 1980.

9. Hoeppler, T., Hendrickson, P., Dietrich, C., and Reme, C.: Morphology and time course of defined photochemical lesions in the rabbit retina. Curr. Eye Res. 7:849, 1988.

10. Chandler, D. B., Quansah, F. A., Hida, T., and Machemer, R.: A refined experimental model for proliferative vitreoretinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 224:84, 1986.

11. Ham, W. T., Ruffolo, J. J., Mueller, H. A., Clarke, A. M., and Moon, M. E.: Histologic analysis of photochemical lesions produced in the rhesus retina by short wavelength light. Invest. Ophthalmol. Vis. Sci. 17:1029, 1978.

12. Machemer, R.: Experimental retinal detachment in the owl monkey. II. Histology of retina and pigment epithelium. Am. J. Ophthalmol. 66:396, 1968.

13. Kroll, A. J., and Machemer, R.: Experimental retinal detachment in the owl monkey. III. Electron microscopy of retina and pigment epithelium. Am. J. Ophthalmol. 66:410, 1968.

14. Ham, W. T., Mueller, H. A., Ruffolo, J. J., Millen, J. E., Cleary, S. F., Guerry, R. K., and Guerry, D.: Basic mechanisms underlying the production of photochemical lesions in mammalian retina. Curr. Eye Res. 3:165, 1984.

Correlation Between Intraocular Pressure Control and Progressive Glaucomatous Damage in Primary Open-Angle Glaucoma

Lisa Kay Mao, M.D., William C. Stewart, M.D., and M. Bruce Shields, M.D.

Fifty-five patients with primary open-angle glaucoma and early glaucomatous damage who had medical therapy and laser trabeculoplasty were followed up for four to 11 years or until progressive glaucomatous damage was documented. Factors associated with the stability or progression of glaucoma were evaluated. Eyes with mean intraocular pressure higher than 21 mm Hg during the follow-up period uniformly had progressive glaucomatous changes. Conversely, eyes with mean intraocular pressure less than 17 mm Hg remained stable, and approximately half of the eyes with mean intraocular pressure between 17 and 21 mm Hg had progressive glaucomatous changes. Patients who remained stable were slightly younger than those with progressive glaucomatous changes ($P < .05$), but initial optic nerve head appearance, initial visual field findings, number of medicines used, medical history, and patient gender or race were not statistically associated with stability or progression of the glaucoma. These findings reinforce the importance of intraocular pressure control in primary open-angle glaucoma and the need to identify other markers that help determine the proper level of intraocular pressure for individual patients.

PRIMARY OPEN-ANGLE GLAUCOMA generally is managed by decreasing the intraocular pressure to a level that the physician believes will prevent further damage to the optic disk and loss of visual field. Previous studies suggest that patients with glaucomatous damage require an intraocular pressure within the normal range to prevent progression. Few specific criteria exist, however, to help the physician decide how low the intraocular pressure should be for each individual patient.

We studied patients with primary open-angle glaucoma with relatively early glaucomatous damage whose intraocular pressures were controlled medically or with the addition of laser trabeculoplasty to a level that was believed would prevent progression. We wished to determine what intraocular pressure level would actually prevent progression of the disease in these patients and what additional factors might help in determining adequate treatment.

Patients and Methods

We studied the records of patients with primary open-angle glaucoma treated by the glaucoma service at the Duke University Eye Center between 1976 and 1987. Each patient was examined by one of us (M.B.S.) at each outpatient visit.

Patients included in this study had intraocular pressure controlled only by medical therapy or with argon laser trabeculoplasty. All patients had glaucomatous optic atrophy, whereas the visual field was either normal or showed sensitivity loss isolated to one hemifield. One eye was chosen randomly to be examined for this study.

We excluded patients with congenital, closed-angle, or secondary glaucomas, and those who had previous intraocular procedures. Also excluded were patients with retinal or neurologic disease as well as those with reduced clarity of the ocular media that might have interfered with the optic nerve head or visual field examination. We also did not include patients who were poorly compliant in

Accepted for publication Oct. 3, 1990.

From the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina (Drs. Mao and Shields), and Department of Ophthalmology, Medical University of South Carolina, Charleston, South Carolina (Dr. Stewart).

Reprint requests to William C. Stewart, M.D., Storm Eye Institute, 171 Ashley Ave., Charleston, SC 29425.

administering their medical therapy or in keeping outpatient appointments.

Patients were followed up at four-month intervals or more frequently as needed. At each outpatient visit intraocular pressure was measured with Goldmann applanation tonometry. Also, examination of the ocular adnexa, slit-lamp biomicroscopy, and an optic disk examination were performed. Dilated optic disk and visual field examinations were completed yearly or more frequently as needed.

The optic disk was examined by stereoscopic techniques including both the Hruby lens and color photographs. At each examination the optic disk was described by the horizontal cup/disk ratio and by location of any neural rim thinning (that is, notching or saucerization). Criteria for progression of the optic disk included an increase in the cup/disk ratio by 0.2 or greater or a localized loss of rim tissue that was consistently observed for at least three successive examinations.

The initial visual field was interpreted as either being nonglaucomatous (that is, normal or having only nonspecific changes) or glaucomatous. A glaucomatous field was classified further as having early arcuate nerve fiber layer changes (that is, paracentral or Seidel's scotoma or nasal step) or late arcuate nerve fiber layer changes (that is, arcuate scotoma). The diagnoses of the inferior and superior hemifields were made separately.

Criteria for progression of a normal visual field included the development of nerve fiber layer changes that were noted consistently for at least three successive examinations. Criteria for progression of a visual field with early nerve fiber layer changes included progression to an arcuate scotoma or development of a new nerve fiber layer defect in the opposite hemifield that was observed for at least three successive visual field examinations. The criterion for progression of the visual field in patients with an arcuate scotoma was the eventual development in the opposite hemifield of a nerve fiber layer defect noted for at least three successive examinations. Visual field examinations were performed during the early years of the study on the Goldmann perimeter and later on the Octopus automated perimeter. A diagnosis of progression of the disease was only made when comparing visual fields from either manual or automated perimetry.

Data were recorded until a patient showed either glaucomatous progression in the optic nerve head or visual field, or if no progression was observed, for as long as the records were available. Patients were followed up for a minimum of four years unless they showed progression before this time.

The data were analyzed by dividing the patients' condition into a category of either stable disease or progressed disease. The average and peak intraocular pressures during the follow-up interval and the average age of patients when first examined were compared between the two groups by using the Student's *t*-test. Differences between groups in the distribution of the initial cup/disk ratio and visual field defects, number of medicines used, medical history, race, and sex were assessed with the chi-square test.

Results

Of 55 patients with primary open-angle glaucoma, the disease remained stable in 27 patients throughout the study and progressed in 28 patients. All but one of the patients whose disease progressed had an increase in optic atrophy, and half of these patients also had visual field progression, whereas only one patient had visual field progression without apparent disk change.

In the group with stable disease, the mean age of the patients was 62.8 ± 11.8 years (range, 32 to 82 years). There were nine men and 18 women. Twenty-four patients were white and three were black. The average number of medicines used by the patients was 2.6.

In the group with progressed disease, the mean age of the patients was 72.2 ± 12.2 years (range, 37 to 90 years). There were ten men and 18 women. Twenty-seven patients were white and one was black. The average number of medicines used by the patients was 2.6.

Systemic medical disease in patients with progressed disease included cardiovascular disease in seven patients, arthritis in three patients, gout in one patient, and thyroid disease in one patient. In patients in whom the disease remained stable, cardiovascular disease, arthritis, depression, and diabetes mellitus each afflicted one patient. The only significant difference between these groups was that patients in whom the disease remained stable had a lower mean age than those in whom the disease progressed ($P < .01$). Both groups, however, had a similar range of patient ages.

Of the 27 patients in whom the disease re-

mained stable, initial examination showed no visual field defects in 19 patients, an incomplete arcuate scotoma in two patients, and an arcuate scotoma in six patients. The cup/disk ratios at the initial examination were 0.5 in three patients, 0.6 in one patient, 0.7 in 12 patients, 0.8 in seven patients, 0.9 in three patients, and total cup in one patient.

Of the 28 patients in whom the disease progressed, initial examination showed no visual field defects in 18 patients, an incomplete arcuate scotoma in seven patients, and an arcuate scotoma in three patients. The cup/disk ratios at the initial examination were 0.6 in two patients, 0.7 in 12 patients, 0.8 in ten patients, and 0.9 in four patients. No significant differences existed between groups for either of these parameters ($P > .05$).

In the group with stable disease, the mean intraocular pressure was 17.5 ± 2.3 mm Hg with a peak of 22.8 ± 6.5 mm Hg. There were no progressive optic nerve or visual field changes. The mean follow-up interval was 7.0 ± 2.0 years (range, 4.0 to 11.0 years).

In the group with progressive disease, the mean intraocular pressure was 20.4 ± 2.3 mm Hg with a peak of 27.2 ± 5.4 mm Hg. There were 27 patients with progressive optic nerve changes and 15 patients with progressive visual field changes. The mean follow-up interval was 3.8 ± 2.2 years (range, 1.0 to 10.0 years). Eyes that remained stable had a statistically lower mean ($P < .005$) and peak ($P < .01$) intraocular pressure than those that progressed. The Figure shows the mean intraocular pressure and number of patients in whom the disease progressed or remained stable during the follow-up period. In no patient did the disease remain stable with an average intraocular pressure of greater than 21 mm Hg, and in no patient did the disease progress with a mean intraocular pressure of less than 17 mm Hg. Approximately half of the patients with intraocular pressure between 17 and 21 mm Hg showed progression of the disease. Additionally, patients who had a peak intraocular pressure of less than 20 mm Hg did not show progression of the disease. No level of peak intraocular pressure, however, was noted above which the disease progressed uniformly.

Discussion

Controversy still exists over the proper treatment of primary open-angle glaucoma. In general, therapy consists of using medical and then surgical therapy as needed to decrease the intraocular pressure to a level that the physician believes will prevent progressive glaucomatous damage. Unfortunately, little data exist that help the physician determine the adequacy of treatment for primary open-angle glaucoma.

Chandler[1] and Shaffer[2] indicated that in patients with advanced glaucomatous changes, intraocular pressure should be kept in a normal range to prevent progressive visual field damage. Kolker[3] subsequently showed that in patients with a visual field cut to within 5 degrees of fixation, only 4% of eyes that maintained an intraocular pressure of 18 mm Hg or less showed progression of disease. A study by Quigley and Maumenee[4] reinforced the importance of intraocular pressure reduction in patients with visual field defects close to fixation, and other reports have implied that the disease in patients with advanced visual field loss and intraocular pressure of 15 mm Hg or less usually remains stable.[5,6]

Conversely, patients with limited glaucomatous damage possibly may tolerate a higher intraocular pressure than those with advanced disease.[7-9] Data from one study suggested that the disease in patients with visual field loss isolated to either the superior or inferior hemifield usually remained stable with intraocular pressure of 18 mm Hg or less.[5] In patients with only optic disk damage and without visual field loss, intraocular pressure of 22 mm Hg or less may be adequate.[5] Kass, Kolker, and Becker[10] studied patients with bilateral increase of intraocular pressure and unilateral field loss. When the initial intraocular pressure was higher than 26 mm Hg in the eye without visual field loss, progressive glaucomatous damage occurred ten times more frequently than when it was less than that level.

Although decreasing the intraocular pressure generally helps to prevent further glaucomatous damage, prescribing treatment to a preselected intraocular pressure does not always guard against progression.[10] Unfortunately, besides intraocular pressure, little information is available concerning other factors that help determine whether a disease is likely to progress or remain stable. Wilson and associates[11] noted that apart from initial intraocular pressure, the disease in female patients and those with a family history of glaucoma and advanced glaucomatous visual field defects is more likely to progress. Spaeth[12] and Spaeth and associates[13] stated that an improvement in the appear-

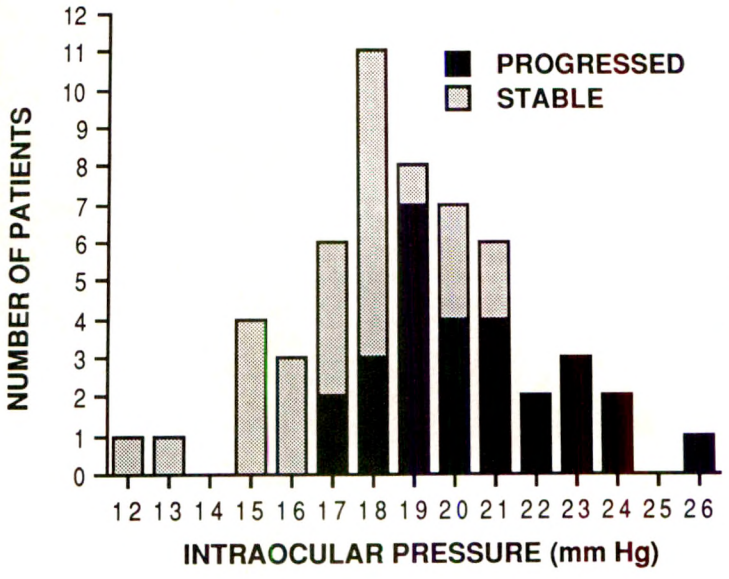


Figure (Mao, Stewart, and Shields). Mean intraocular pressure of patients who remained stable or had progressive glaucomatous changes during the follow-up period.

ance of the optic nerve head or visual field examination upon therapeutic decreasing of intraocular pressure potentially may be useful in determining the sufficiency of glaucoma therapy.

We wished to determine clinical markers that help show the adequacy of treatment for patients with limited damage from primary open-angle glaucoma. We studied a group of patients with limited visual field changes because of past evidence that suggested patients with more advanced damage may have different requirements for intraocular pressure control.[5] We used both changes in the optic nerve head and the visual field to determine progression or stability of the primary open-angle glaucoma. Previous studies have used only the visual field to determine progression of the disease. We studied the optic nerve head for signs of progression since damage to the neural rim has been shown to be an important early diagnostic characteristic of glaucoma.[14,15]

Our study showed that of the patients in whom the disease remained stable over the follow-up period, none had an average intraocular pressure greater than 21 mm Hg. Conversely, for those patients in whom the disease progressed, all had an average intraocular pressure of 17 mm Hg or greater and a peak intraocular pressure of 20 mm Hg or higher. In patients with an average intraocular pressure between 17 and 21 mm Hg, the disease remained stable in approximately one half of the patients over the follow-up period. Potentially with a longer follow-up interval the disease would have progressed in more of these patients.

Neither the initial cup/disk ratio, presence or type of visual field loss, number of medicines used, medical history, sex, or race of the patient helped to identify those in whom the disease would progress or remain stable. Patients in whom the disease did not progress, however, had a slightly younger age than those in whom the disease progressed. This is consistent with previous reports that indicated advanced age was a risk factor for glaucomatous damage.[16,17] However, no age group was safe from glaucomatous progression.

Our results differ from one study of patients with limited glaucomatous damage in that our patients required a slightly lower intraocular pressure to prevent glaucomatous progression.[5] This difference may have resulted because we used changes in the optic nerve head as a criterion for progression as well as the visual field. In our patients only approximately half of the eyes that showed glaucomatous optic disk progression also demonstrated worsening of the visual field. If the visual field examinations had been used alone as a measure of progression, the level of intraocular pressure that would have indicated control may have been higher than shown in this study.

Our study reinforces the importance of decreasing the intraocular pressure and examining the optic nerve head in patients with primary open-angle glaucoma. We did not identify, however, other markers that help determine the proper level of medical or surgical

treatment to prevent progression. More study is required to gain the knowledge that will help determine a proper treatment regimen in patients with primary open-angle glaucoma. Continued evaluation of data from long-term follow-up of patients with primary open-angle glaucoma and the investigation of newer techniques in optic nerve head analysis and retinal sensory testing may help achieve this goal.

References

1. Chandler, P. A.: Long-term results in glaucoma therapy. The Sanford R. Gifford Lecture. Am. J. Ophthalmol. 49:221, 1960.
2. Shaffer, R. N.: Open-angle glaucoma. Trans. Am. Acad. Ophthalmol. Otolaryngol. 67:467, 1963.
3. Kolker, A. E.: Visual prognosis in advanced glaucoma. A comparison of medical and surgical therapy for retention of vision in 101 eyes with advanced glaucoma. Trans. Am. Ophthalmol. Soc. 75:539, 1977.
4. Quigley, H. A., and Maumenee, A. E.: Long-term follow-up of treated open-angle glaucoma. Am. J. Ophthalmol. 87:519, 1979.
5. Grant, W. M., and Burke, J. F.: Why do some people go blind from glaucoma? Ophthalmology 89:991, 1982.
6. Odberg, T.: Visual field prognosis in advanced glaucoma. Acta Ophthalmol. 65:27, 1987.
7. Werner, E. B., and Drance, S. M.: Progression of glaucomatous field defects despite successful filtration. Can. J. Ophthalmol. 12:275, 1977.
8. Kronfeld, P. C., and McGarry, H. I.: Five year follow-up of glaucomas. JAMA 136:957, 1948.
9. Fruhauf, A., Muller, F., and Sismuth, M.: Investigation about the prognosis of glaucoma. Klin. Monatsbl. Augenheilkd. 151:477, 1967.
10. Kass, M. A., Kolker, A. E., and Becker, B.: Prognostic factors in glaucomatous visual field loss. Arch. Ophthalmol. 94:1274, 1976.
11. Wilson, R., Walker, A. M., Ducker, D. K., and Crick, R. P.: Risk factors for rate of progression of glaucomatous visual field loss. A computer-based analysis. Arch. Ophthalmol. 100:737, 1982.
12. Spaeth, G. L.: Control of glaucoma. A new definition. Ophthalmic Surg. 14:303, 1983.
13. Spaeth, G. L., Fellman, R. L., Starita, R. L., Katz, L. J., and Poryzees, E. M.: A new management system for glaucoma based on improvement of the appearance of the optic disc or visual field. Trans. Am. Ophthalmol. Soc. 83:268, 1985.
14. Quigley, H. A., Addicks, E. M., and Green, W. R.: Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch. Ophthalmol. 100:135, 1982.
15. Quigley, H. A.: Glaucoma's optic nerve damage. Changing clinical perspectives. Ann. Ophthalmol. 14:611, 1982.
16. Kurland, L. T., and Taub, R. G.: The frequency of glaucoma in a small urban community. Am. J. Ophthalmol. 43:539, 1957.
17. Wright, J. E.: The Bedford glaucoma survey. In Hunt, L. B. (ed.): Glaucoma. Epidemiology, Early Diagnosis and Some Aspects of Treatment. Edinburgh, E & S Livingstone Ltd., 1966, pp. 12–17.

OPHTHALMIC MINIATURE

While I waited for him to finish one of his stories, I took time to memorize his features. He belonged to the same blue-eyed stock of his wife, but his were flecked with green; they changed color or seemed to when they caught the sunlight pouring into the room from the back yard.

Pat Conroy, *The Prince of Tides*
New York, Bantam Books, 1986, p. 238

Increased Intraocular Pressure in Severely Burned Patients

Lawrence S. Evans, M.D.

Six eyes of three patients with severe body burns had intraocular pressure ranging from 37.2 to 81.7 mm Hg. Because of extreme orbital congestion, lateral canthotomies were performed, which caused abrupt decrease in intraocular pressure (range, 17.6 to 49.0 mm Hg). None of the patients had a history of glaucoma, narrow angles, or any precondition for a pupillary block mechanism. Two patients survived and neither had optic nerve damage or increased intraocular pressure after hospital discharge. Tonometry should be performed in patients with severe burns and orbital congestion, especially in those patients receiving large amounts of intravenous fluids. Lateral canthotomies may be of benefit to relieve potentially damaging high intraocular pressure.

EYELID BURNS are the most common ocular injuries seen in serious thermal burn accidents, which are most frequently house fires and flash fires of combustible vapors and gases. The globes tend to be spared, although minor corneal abrasions are often seen. I treated three patients with severe burns who had high intraocular pressure. Lateral canthotomies lowered the intraocular pressure immediately, which implicated swollen periocular tissues pressing on the globes as the main reason for the intraocular pressure increase.

Case Reports

Case 1

A 59-year-old man was admitted to the burn unit of Loyola University Medical Center after an explosion and flash fire in an industrial accident. The patient had second- and third-degree burns of the face, lower extremities, back, and forearms, totaling 55% of the body surface. The eyes had clear corneas, moderately chemotic conjunctivae, normal pupillary light reflexes, partial-thickness eyelid burns, and singed eyelashes. Between the time of admission and the time of the follow-up examination (30 hours), the patient received 32.2 l of intravenous fluids, 80 ml of oral antacids, with 4.2 l of urine output, for a measured excess input over output of approximately 28 l of fluids. His body weight was 77.3 kg at admission and 93.0 kg at the time of the follow-up examination, for a gain of 15.7 kg. This gain was less than that of the fluid excess, but this was expected because of the fluid loss through burned areas. At this time, the face was greatly swollen and the eyelids were tight. Schiötz tonometry measurements were taken without pressing on the globes and were found to be 37.2 mm Hg in each eye. The patient had no previous ocular problems, and there was no reason to suspect a bilateral pupillary block mechanism for the intraocular pressure increase. Permission was obtained from the patient's family to perform lateral canthotomies. The lateral canthal areas were injected with 2% lidocaine with epinephrine, and lateral canthotomies were performed. Intraocular pressure, measured immediately, was R.E.: 29.4 mm Hg and L.E.: 19.6 mm Hg. The patient had a lengthy convalescence and was fully ambulatory without visual complaints six months after the accident. Visual acuity was R.E.: 20/20 with refraction of +1.00 +1.25 × 5 and L.E.: 20/20 with refraction of +1.00 +0.75 × 2. Results of slit-lamp examination of the corneas, anterior chambers, irides, and conjunctivae were normal. No canthotomy scars were discernible. The eyelid burns were healed entirely and the eyelashes had regrown without misdirection. Intraocular pressure was R.E.: 13 mm Hg and L.E.: 17 mm Hg by applanation tonometry. Results of Goldmann visual field testing were full to I_{3e} and I_{4e}. Results of examination of the optic nerves and the remainder of the fundus examination were normal.

Accepted for publication Sept. 26, 1990.

From the Department of Ophthalmology, Stritch School of Medicine, Loyola University of Chicago, Maywood, Illinois.

Reprint requests to Lawrence S. Evans, M.D., Department of Ophthalmology, Stritch School of Medicine Loyola University of Chicago, 2160 S. First Ave., Maywood, IL 60153.

Case 2

A 72-year-old man received burns over 30% of his body surface and inhalational injuries in a house fire. The patient had partial-thickness burns of the forearms, left upper arm and shoulder, the anterior surface of the entire left leg, and of the back of the head. He had a full-thickness burn of the face. The family stated that he had diabetes mellitus and hypertension but no previous ocular problems. The patient was comatose and pharmacologically paralyzed for mechanical respiratory ventilation when examined three hours after admission for ophthalmic assessment. Both corneas were cloudy, and a central epithelial defect was noted on the right eye. The left conjunctiva was chemotic. Pupils were 1.5 mm in size and unreactive in both eyes. When re-examined 20 hours later, the eyelids were swollen and tight. Intraocular pressure was R.E.: 74.0 mm Hg and L.E.: 72.0 mm Hg. Lateral canthotomies were performed. Intraocular pressure, measured immediately, was R.E.: 35.0 mm Hg and L.E.: 30.0 mm Hg. By the time the canthotomies were performed, the patient received 23 l of intravenous fluids and had a urine output of 2 l for a measured fluid gain of 21 l in 23 hours. The patient's condition deteriorated, and he died six days later.

Case 3

A 27-year-old man received high-voltage electric burns in a highway construction accident. Ocular examination in the emergency room showed a central epithelial defect on the right cornea and a total epithelial defect on the left cornea. Both corneas were hazy, and moderate chemosis was noted in both eyes. The pupils were not dilated at the request of the admitting service. Upon admission the patient was taken to the operating room for fasciotomies on all extremities. At this time, approximately four hours after admission, intraocular pressure, measured by Schiötz tonometry, was R.E.: 81.7 mm Hg and L.E.: 50.2 mm Hg. Lateral canthotomies were performed, and intraocular pressure, measured immediately afterward, was R.E.: 32.2 mm Hg and L.E.: 24.4 mm Hg. When the canthotomies were performed, the patient received approximately 7.6 l of intravenous fluids and had a urine output of 1.9 l, for a measured gain of 5.7 l. The severity of the injury necessitated amputation of both arms, total skin grafting to the face, and several reconstructive procedures of the eyelids, with further surgical procedures foreseen. Five months after the injury, intraocular pressure was 16.0 mm Hg in each eye. The patient developed bilateral cataracts with best-corrected visual acuity of 20/60 in each eye. The optic nerves appeared to have a normal myopic configuration, corresponding to the patient's refractive error. Seventeen months after the injury when the eyelids had healed sufficiently, the left cataract was removed and a posterior chamber intraocular lens was implanted, which resulted in 20/20 visual acuity.

Discussion

The administration of large quantities of intravenous fluids to maintain blood pressure is the key therapeutic measure in treatment of the severely burned patient, and this contributes to the orbital congestion. In the patient in Case 3, for example, 31 l of fluids was given within 24 hours of the injury. Continuous cardiovascular monitoring, including the use of intracardiac catheters, is necessary to provide close pharmacologic support. All three patients had massive periorbital swelling, and because each eye showed a marked decrease in intraocular pressure when lateral canthotomy was performed, it is evident that orbital pressure transmitted to the eye was the primary mechanism for the high intraocular pressure. That none of the eyes had normal intraocular pressure after canthotomy may be attributed, at least in part, to incompleteness of the canthotomies and residual high orbital pressure. Two patients received large amounts of intravenous fluids, and the third patient received a moderate amount. Therefore, fluid loading does not appear to be the sole reason for the high orbital pressure. Another plausible mechanism to consider for the intraocular pressure increase is pupillary block caused by orbital pressure on the globe, displacing the lens anteriorly. Electric burns, such as those seen in the patient in Case 3, are also thermal burns because body resistance to electric current converts electric energy into heat.[1] Small controlled electric currents, however, such as those used for electroshock therapy[2] and cardioversion,[3] have been reported to cause increased intraocular pressure.

A general feature of severe burn injury is the shift of water from the intravascular space to the extravascular space, particularly to the periocular extravascular space, which can cause swelling and tightness of the eyelids. Water is

also lost through burned body surfaces. These processes may lead to dangerous hypotension and hemoconcentration. Administration of large volumes of sodium-containing intravenous fluids is necessary to maintain hemodynamics and to correct electrolyte imbalances.[1] Several factors contribute to the extracellular edema, including the following: increased capillary endothelial leakage, which permits water and plasma proteins to enter the extracellular space; reduction in capillary colloid osmotic pressure from decreased plasma protein concentration; increased capillary hydrostatic pressure from vasoconstriction or capillary blockage by platelets or cells; and impaired lymphatic drainage from duct blockage by platelets, cells, or both.[1] Severe derangements of fluid and electrolyte imbalance usually occur, generally caused by systemic impairment of the cellular sodium-potassium pump.[1] Endocrine responses to burn injury include high levels of antidiuretic hormone and aldosterone, which promote fluid retention, possibly potentiating orbital congestion.[1]

Typically the severely burned patient does not develop periorbital edema until a few hours after the injury. Immediate examination facilitates evaluation of any ocular injuries. This examination may precede an intraocular pressure increase, so it is important to perform tonometry after periorbital edema ensues. Periorbital edema may occur even when the face is spared from a direct burn. On arrival at the hospital, many severely burned patients are able to cooperate for ocular examination, possibly to relate previous ocular problems and to permit measurement of visual acuity with a near-vision test card. Severely burned patients are usually pharmacologically paralyzed and given mechanical pulmonary ventilation with endotracheal intubation shortly after arrival, which limits cooperation for examination, even though they may be fully conscious and aware. The eyelids and conjunctival sacs should be irrigated to remove particulate material. Singed eyelashes may be removed with a moist sponge to prevent them from entering and irritating the eyes. Eyelid retraction is necessary for examination if periorbital edema has already developed. After the cornea is examined, tonometry is performed with retraction relaxed to permit a more accurate reading. Topical anesthesia should be used because the patient may have full sensation even though unable to communicate. If high intraocular pressure is found with severe periocular edema and canthotomy is to be performed, local anesthesia should be injected through unburned skin if possible. An ophthalmic antibiotic ointment should be applied to the globes and canthotomy sites. Silver sulfadiazine is commonly used to treat burned skin when there is no known allergy to sulfonamides. Sulfacetamide 10% ophthalmic ointment may also be used without increased risk of allergic reaction. Aminoglycoside antibiotics should be avoided to lessen the chance of emergence of resistant strains of bacteria.

Fuchs[4] reported that acute transitory glaucoma can occur with thermal burns, but this refers to direct burns of the eye and adnexa. In 11 previously described patients with blindness after major burns with variable degrees of recovery in four patients, Resch and Sullivan[5] remarked that in five of the six adult patients the optic nerves were either pale or edematous. They did not mention increased intraocular pressure as a possible factor. All patients had other significant ophthalmic and neurologic signs. Salz and Donin[6] and Walsh and Hoyt[7] have also described similar patients.

References

1. Davies, J. W. L.: Physiological Responses to Burn Injury. London, Academic Press, 1982, pp. 13; 46; 212; 215; 532; and 537.

2. Arstikaitis, M., and Hodgson, H.: The effect of lobotomy and electroshock on intraocular pressure. Am. J. Ophthalmol. 35:1625, 1952.

3. Berger, R. O.: Ocular complications of cardioversion. Ann. Ophthalmol. 10:161, 1978.

4. Fuchs, H. E.: Textbook of Ophthalmology, ed. 7. Philadelphia, J. B. Lippincott, 1923, pp. 498 and 785.

5. Resch, C. S., and Sullivan, W. G.: Unexplained blindness after a major burn. Burns 14:225, 1988.

6. Salz, J. J., and Donin, J. F.: Blindness after burns. Can. J. Ophthalmol. 7:243, 1972.

7. Walsh, F. B., and Hoyt, W. F.: Clinical Neuro-Ophthalmology, ed. 3. Baltimore, Williams and Wilkins, 1969, pp. 2480–2482.

The Effect of Perkins, Tono-Pen, and Schiötz Tonometry on Intraocular Pressure

Marc M. Whitacre, M.D., Mark Emig, M.D., and Khatab Hassanein, Ph.D.

We studied the intraocular pressure changes produced in five eye bank eyes by Perkins, Tono-Pen, and Schiötz tonometry performed by experienced and inexperienced personnel. When all users were considered together, Perkins tonometry produced a mean intraocular pressure increase of 0.7 mm Hg, significantly less than the mean increase of 12.1 mm Hg produced by Tono-Pen tonometry ($P < .05$) or the mean increase of 16.5 mm Hg produced by Schiötz tonometry ($P < .01$). There was no statistically significant difference between the intraocular pressure increase produced by Tono-Pen or Schiötz tonometry. Tonometry performed by inexperienced Tono-Pen users and experienced or inexperienced Schiötz users produced a significantly greater increase in intraocular pressure than that performed by experienced Tono-Pen users ($P < .05$), and an extremely significant increase compared to tonometry performed by experienced or inexperienced Perkins users ($P < .01$). The marked increase in intraocular pressure produced by Tono-Pen tonometry suggests that hand-held electronic applanation tonometers should be used with caution in eyes with a weakened cornea or sclera.

Assessment of intraocular pressure in eyes after surgery, blunt or penetrating injuries, or the onset of a medical condition that weakens the cornea or sclera is desirable. When irregular corneal astigmatism, corneal edema, or corneal scarring are present the small applanating area of the Mackay-Marg tonometer[1-3] or Tono-Pen[4,5] may provide more accurate intraocular pressure readings than Goldmann or Perkins applanation tonometry. In recent years the Tono-Pen has been used increasingly to assess intraocular pressure in eyes after penetrating keratoplasty, repaired corneal lacerations, or other ocular conditions associated with irregular astigmatism, including peripheral corneal degenerations. The use of the Tono-Pen in gas-containing eyes after pars plana vitrectomy has also been suggested.[6,7] The intraocular pressure changes caused by Schiötz tonometry[8-10] and Goldmann applanation tonometry[11,12] have been measured or calculated. The increase caused by Mackay-Marg or Tono-Pen electronic applanation tonometers has never been measured or calculated. We investigated the intraocular pressure changes caused by the use of the Perkins, Tono-Pen, and Schiötz tonometers in eye bank eyes.

Material and Methods

Eye bank eyes were selected from donors not believed to have any ocular diseases. The eyes were used within 24 hours of death of the donor, and all had intact corneal epithelium and clear corneal stroma. Only one eye per donor was used. The eyes were placed in a small metal cup lined with wet cotton, and a 21-gauge needle was inserted through the corneoscleral limbus. A short length of tubing connected the needle to one arm of a three-way stopcock. A transducer was connected to the needle by one arm of the three-way stopcock. The transducer output was amplified by an amplifier, which was in turn connected to a storage oscilloscope. A bag of normal saline attached to a manometer was connected to the third arm of the stopcock. All air bubbles present within the tubing and stopcocks were purged. The stopcock was closed so that the eye was removed from the

Accepted for publication Oct. 2, 1990.

From the Departments of Ophthalmology (Drs. Whitacre and Emig) and Biometry (Dr. Hassanein), University of Kansas Medical Center, Kansas City, Kansas. This study was supported by an unrestricted grant from Research to Prevent Blindness, Inc., and the Kansas Lions Sight Foundation.

Reprint requests to Marc M. Whitacre, M.D., Department of Ophthalmology, Sudler Hall, University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, KS 66103.

circuit, and the calibration of the pressure transducer was verified by varying the height of the bag of saline and comparing the transducer reading to the manometer. The rigidity of the measurement system (with the eye removed from the circuit) was measured and found to be 1 μl^{-1}. The dynamic response time of the system to changing pressure was measured by reducing the pressure on the transducer to zero, then abruptly opening the stopcock to increase the pressure on the transducer to 40 mm Hg. Examination of the triggered sweep of the storage oscilloscope showed that complete equilibration from a pressure of 0 mm Hg to a pressure of 40 mm Hg occurred within 50 milliseconds.

Each eye was subjected to an identical experimental procedure. Once connected to the apparatus, the intraocular pressure in the eye was increased to 16 mm Hg, and the limbal needle insertion site was checked for leaks. No leaks that caused a detectable disturbance in the intraocular pressure within 15 seconds were found. The eye was left undisturbed, and the stopcock to the eye closed, which isolated it from the bag of saline and the manometer. The recording oscilloscope was triggered, and a photograph was taken of this control procedure (Fig. 1). The tonometry procedures were then performed. Before each procedure the stopcock was reopened to restore the intraocular pressure to precisely 16 mm Hg. The cornea was moistened with saline, and the stopcock was then closed. The recording oscilloscope was triggered, and tonometry was performed on the eye by either a staff ophthalmologist or an ophthalmology resident. A photograph of the oscilloscope display was taken. This procedure was repeated three times with each tonometry instrument by both experienced and then inexperienced users.

The tonometric procedures were always performed in the same order. Perkins applanation tonometry was done first by an experienced and then by an inexperienced staff ophthalmologist or ophthalmology resident. This was followed by Tono-Pen tonometry, done by an experienced and then by an inexperienced ophthalmologist or ophthalmology resident, followed by Schiötz tonometry done in the same fashion. Personnel were deemed experienced if they were knowledgeable in the operation of the tonometer and had used the tonometer more than 50 times in a clinical setting. Personnel were deemed inexperienced if they were familiar with the operation of the tonometer and had used the device more than ten but less than 50 times in a clinical setting. None of the personnel recruited by the experimenters knew the purpose of the study. Before performing tonometry, the users were told to make themselves comfortable and support their hand or hands to make the tonometer steady. All were told to use their usual tonometric method. None were told what intraocular pressure was present within the eye to be tested. Users of the Perkins tonometer were told to set the Perkins tonometer to a pressure slightly above 0 mm Hg, so the applanating prism was extended before attempting tonometry. Schiötz tonometry was performed with the 5.5-g weight. When Perkins and Schiötz tonometry were performed, a single measurement was recorded per sweep of the storage oscilloscope (ten seconds). When Tono-Pen tonometry was performed, tonometry was not stopped until four satisfactory measurements were obtained (as indicated by the audible beep) or the attempt at tonometry required more than ten seconds, at which time the user was instructed to halt. Because the Tono-Pen can take two readings from each contact with the eye, a minimum of two contacts with the eye were necessary to obtain four satisfactory measurements. Personnel were rotated between tonometry devices and eyes so that none of the recruited personnel did more than one tonometry procedure to a single eye or more than two of the same procedure in the entire study.



Fig. 1 (Whitacre, Emig, and Hassanein). The intraocular pressure change produced by a control procedure. The top line is the intraocular pressure recorded by the transducer, unchanging at 16 mm Hg. The bottom line is the reference line indicating 0 mm Hg. The tracing records a ten-second interval.

After completion of the tonometric procedures, the needle insertion site was rechecked for leaks. If any leaks were found, the intraocular pressure was reduced to 0 mm Hg, the limbal area gently dried, and the leak sealed with cyanoacrylate glue. The intraocular pressure of each eye was then adjusted to 10 mm Hg, and the coefficient of ocular rigidity of each eye was studied by successively injecting 0.01-

ml aliquots of saline into the eye until an intraocular pressure of approximately 40 mm Hg was reached. The coefficient of rigidity was then calculated for each intraocular pressure change produced by the 0.01-ml injections and averaged to yield an average coefficient of rigidity for that eye. The coefficient of rigidity of the experimental eyes varied from between 0.012 μl^{-1} to 0.015 μl^{-1}, a range within normal limits.[13,14]

Results

Perkins applanation tonometry produced a mean increase of 0.7 mm Hg in the intraocular pressure (Fig. 2). Tonometry performed by experienced users produced a mean pressure increase of 0.9 mm Hg (range, 0.3 to 3.2 mm Hg; S.D., 0.5 mm Hg), and tonometry performed by inexperienced users produced a mean pressure increase of 0.4 mm Hg (range, 0.0 to 0.8 mm Hg; S.D., 0.2 mm Hg).

Tono-Pen tonometry produced a mean increase of 12.1 mm Hg in the intraocular pressure each time the Tono-Pen contacted the eye. Tonometry performed by experienced personnel produced a mean pressure increase of 6.7 mm Hg (range, 0.2 to 26.9 mm Hg; S.D., 4.8 mm Hg) each time the tonometer contacted the eye. A mean of 5.4 contacts between the Tono-Pen and the eye were necessary before a final measurement was obtained (Fig. 3). Tonometry performed by inexperienced personnel produced a mean pressure increase of 17.5 mm Hg (range, 0.5 to 52.6 mm Hg; S.D., 16.7 mm Hg). A mean of 9.5 contacts were necessary before a final measurement was obtained (Figs. 4 and 5).

Schiötz tonometry produced a mean increase of 16.5 mm Hg in the intraocular pressure (Fig. 6). Tonometry performed by experienced users produced a mean pressure increase of 15.9 mm Hg (range, 12.1 to 21.5 mm Hg; S.D., 2.4 mm Hg), and tonometry performed by inexperienced users produced a mean pressure increase of 17.0 mm Hg (range, 14.1 to 20.3 mm Hg; S.D., 1.6 mm Hg).

An analysis of variance for repeated measurements was used to analyze the data. A significant difference ($P = .0052$) was found between the mean intraocular pressure increases caused by Perkins, Tono-Pen, and Schiötz tonometry. Duncan's multiple comparison test was used to locate the statistical difference between the means of the intraocular pressure increases produced by the different tonometry methods when experienced and inexperienced users were considered together and when experienced and inexperienced users were considered separately. When all users were considered together, Perkins tonometry produced a significantly smaller increase in the intraocular pressure than Tono-Pen tonometry ($P < .05$) or Schiötz tonometry ($P < .01$). There was no statistically significant difference between the intraocular pressure increase produced by application of Tono-Pen or Schiötz tonometers. When experienced and inexperienced users were considered separately, there was no statistically significant difference in the intraocular pressure increase produced by tonometry performed by experienced or inexperienced Per-

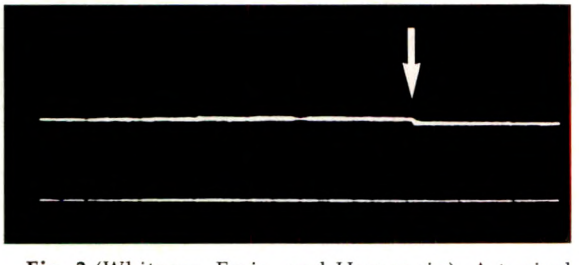


Fig. 2 (Whitacre, Emig, and Hassanein). A typical tracing of the intraocular pressure change produced by Perkins applanation tonometry by experienced or inexperienced users. The top line is the intraocular pressure recorded by the transducer. The bottom line is the reference line indicating 0 mm Hg. The tracing records a ten-second interval. The pressure increase of 0.42 mm Hg produced by the tonometer is most apparent just as the tonometer is removed from the eye (arrow).

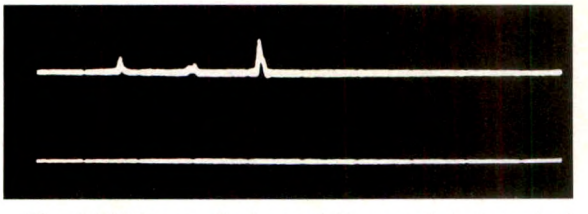


Fig. 3 (Whitacre, Emig, and Hassanein). A typical tracing of the intraocular pressure change produced by Tono-Pen applanation tonometry by an experienced user. The top line is the intraocular pressure recorded by the transducer. The bottom line is the reference line indicating 0 mm Hg. The tracing records a ten-second interval. The tonometer was applied to the eye three times, producing a maximum intraocular pressure increase of 5.6 mm Hg, a minimum intraocular pressure increase of 1.0 mm Hg, and a mean intraocular pressure increase of 2.9 mm Hg per application.



Fig. 4 (Whitacre, Emig, and Hassanein). An example of the intraocular pressure change produced by Tono-Pen applanation tonometry by an inexperienced user. The top line is the intraocular pressure recorded by the transducer. The bottom line is the reference line indicating 0 mm Hg. The tracing records a ten-second interval. The tonometer was applied to the eye 13 times, producing a maximum intraocular pressure increase of 12.0 mm Hg, a minimum intraocular pressure increase of 0.67 mm Hg, and a mean intraocular pressure increase of 5.7 mm Hg per application.

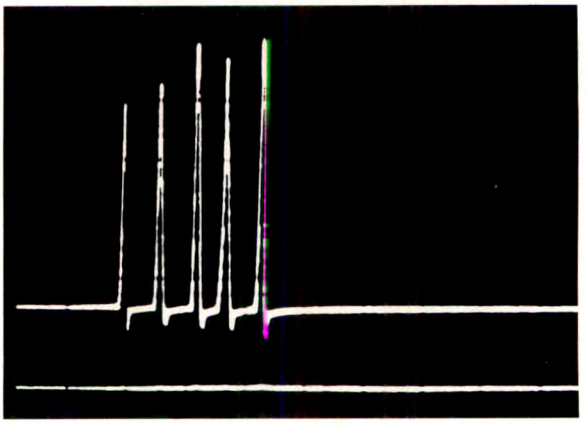


Fig. 5 (Whitacre, Emig, and Hassanein). An example of the intraocular pressure change produced by Tono-Pen applanation tonometry by an inexperienced user. The top line is the intraocular pressure recorded by the transducer. The bottom line is the reference line indicating 0 mm Hg. The tracing records a ten-second interval. The tonometer was applied to the eye five times, producing a maximum intraocular pressure increase of 52.6 mm Hg, a minimum intraocular pressure increase of 39.5 mm Hg, and a mean intraocular pressure increase of 47.1 mm Hg per application.

kins users or experienced Tono-Pen users. Tonometry performed by inexperienced Tono-Pen users produced a significant increase in the intraocular pressure compared to tonometry performed by experienced users ($P < .01$). There was no statistically significant difference in the number of Tono-Pen applications required for experienced or inexperienced users to obtain a full series of measurements. There was no statistically significant difference between the intraocular pressure increase produced by tonometry performed by inexperienced Tono-Pen or experienced or inexperienced Schiötz users.

Discussion

The reasons for the difference in the intraocular pressure increases produced by the different instruments seem clear. In Perkins tonometry the only force against the eye is exerted by the prism of the instrument,[15] unless the user pushes the instrument against the eye far enough to cause the prism to reach the far end of its travel, so the body of the tonometer and the prism are no longer isolated from each other. The applanating prism exerts 1 g of force against the cornea for every 10 mm Hg of indicated pressure on the Perkins tonometer when the zone of applanation has a diameter of 3.06 mm. Unless an eye has an abnormally high coefficient of ocular rigidity or an unusually steep cornea, the application of this force has been calculated to produce an increase in intraocular pressure of less than 1.0 mm Hg if the initial intraocular pressure was 16 mm Hg.[11,12] In our study tonometry performed by inexperienced and experienced users produced only a small increase in intraocular pressure because the spring-loaded prism of the Perkins applanation tonometer has a considerable range of motion. The constant force of the spring throughout this range of motion produces only minimal changes in the intraocular pressure as the user moves the instrument toward or away from the eye. This greatly moderated the effect of user motion on the intraocular pressure and kept the standard deviation of the intraocular pressure increase produced by tonometry performed by experienced or inexperienced users small. We believe that tonometry performed by the inexperienced Perkins users in our study produced a smaller mean increase in the intraocular pressure than tonometry performed by experienced users because inexperienced users did not adjust the tonometer to position the fluorescein rings properly. This may be because the comparatively dim illumination of the prism of the Perkins tonometer makes the inner aspect of the fluorescein ring difficult to appreciate.

Schiötz tonometry substantially increases the intraocular pressure because almost the full

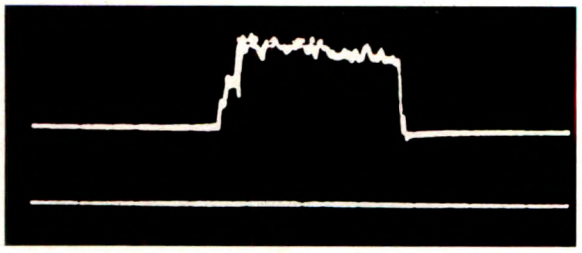


Fig. 6 (Whitacre, Emig, and Hassanein). A typical tracing of the intraocular pressure change produced by Schiötz tonometry by experienced and inexperienced users. The top line is the intraocular pressure recorded by the transducer. The bottom line is the reference line indicating 0 mm Hg. The tracing records a ten-second interval. An intraocular pressure increase of 17.8 mm Hg is recorded.

weight of the instrument rests on the eye. Moses and Becker[8] predicted an increase in the intraocular pressure of 14 mm Hg when a Schiötz tonometer with a 5.5-g weight was applied to eyes of average scleral rigidity and an initial intraocular pressure of 16 mm Hg. Friedenwald[9] estimated an increase of 14.07 mm Hg, and McBain[10] measured an increase of 14.43 mm Hg in the intraocular pressure under similar conditions. Our measurements disclose slightly higher values than these reports, probably because eye bank eyes do not duplicate precisely the intraocular pressure changes a living eye would undergo in response to indentation. The relatively small standard deviation of the intraocular pressure increase produced by the Schiötz tonometer in this study reflects the consistency with which the instrument is applied to the eye by both inexperienced and experienced users.

Hessemer, Rössler, and Jacobi[16] found in their open manometer study of cadaver eyes that corneal indentation interfered with Tono-Pen pressure measurements when the manometric pressure was below 5 mm Hg. Moses, Marg, and Oechsli[17] found it necessary to do open manometer measurements to verify the accuracy of the Mackay-Marg tonometer, which implies that significant ocular volume changes were produced by the application of both these hand-held electronic applanation tonometers.

In our study there were large variations in the amplitude of the intraocular pressure increases produced by Tono-Pen contact with the eye. This occurred for tonometry performed by both experienced and inexperienced users and produced standard deviations of 4.8 and 16.7 mm Hg, respectively, significantly higher than the standard deviations of the Schiötz users. Additionally, there was a difference in the mean number of times the Tono-Pen contacted the eye between the experienced and inexperienced group, although this difference was not statistically significant.

We believe the highly variable and at times marked increases in intraocular pressure produced by Tono-Pen tonometry occur because contact of the eye by this hand-held instrument is not moderated by a spring or other mechanical device. Inexperienced users tend to indent the cornea more than experienced users, occasionally producing substantial increases in intraocular pressure that exceed those produced by Schiötz tonometry and greatly exceed those produced by applanation tonometry. It was not understood by many of our users, especially the inexperienced ones, that only light and brief contact with the eye was required to obtain an intraocular pressure reading (Tono-Pen 2 Tonometer Instruction Manual, Oculab, Glendale, California). Even the most experienced users, some of whom had previously used the Tono-Pen hundreds of times in eye bank eye studies, could not avoid producing marked increases in intraocular pressure some of the time. Because the Tono-Pen can take two readings from each contact with the eye, a minimum of two contacts with the eye is necessary to obtain four satisfactory measurements (and produce the beep). There is a correct technique to touching the Tono-Pen to the cornea that enabled our experienced users to obtain a series of readings with fewer contacts with the eye than the inexperienced group. Inexperienced users needed to contact the eye more times to obtain a reading, which increases the opportunities for producing a marked intraocular pressure increase.

Because of a similar method of operation and use, we believe that similar increases in intraocular pressure would be produced by the Mackay-Marg tonometer. We had a Mackay-Marg tonometer available for use but did not include it in this study because of the absence of personnel experienced in its use.

We conclude that most eyes weakened by surgery or disease seem to tolerate the intraocular pressure increases sometimes produced by this method of tonometry. Our data suggest that hand-held electronic applanation tonometers should be used with circumspection in eyes in which cornea or sclera is weakened markedly. In these eyes it would seem prudent to attempt conventional Goldmann or Perkins applanation tonometry first. If applied to the eye,

the Tono-Pen should be touched gently to the ocular surface. It is probably not necessary to complete a series of four Tono-Pen measurements to estimate the intraocular pressure to a clinically relevant degree of accuracy in the posttrauma or postoperative setting. A single measurement (producing a click) may be all that is needed or warranted. If several contacts with the eye do not yield an audible click indicating a satisfactory pressure measurement, or if a complete series of measurements requires numerous contacts with the eye, the user should consider whether or not the proper technique is being used, and whether or not the knowledge of the intraocular pressure warrants the risk of repeated intraocular pressure increases.

References

1. McMillan, F., and Forster, R. K.: Comparison of Mackay-Marg, Goldmann, and Perkins tonometers in abnormal corneas. Arch. Ophthalmol. 93:421, 1975.

2. Wind, C. A., and Irvine, A. R.: Electronic applanation tonometry in corneal edema and keratoplasty. Invest. Ophthalmol. 8:620, 1969.

3. Kaufman, H. E., Wind, C. A., and Waltman, S. R.: Validity of Mackay-Marg electronic applanation tonometer in patients with scarred irregular corneas. Am. J. Ophthalmol. 69:1003, 1970.

4. Boothe, W., Lee, D. A., Panek, W. C., and Pettit, T. H.: The Tono-Pen. A manometric and clinical study. Arch. Ophthalmol. 106:1214, 1988.

5. Frenkel, R. E. P., Hong, Y. J., and Shin, D. H.: Comparison of the Tono-Pen to the Goldmann applanation tonometer. Arch. Ophthalmol. 106:750, 1988.

6. Hines, M. W., Jost, B. F., and Fogelman, K. L.: Oculab Tono-Pen, Goldmann applanation tonometry, and pneumatic tonometry for intraocular pressure assessment in gas-filled eyes. Am. J. Ophthalmol. 106:174, 1988.

7. Lim, J. I., Blair, N. P., Higgenbotham, E. J., Farber, M. D., Shaw, W. E., and Garretson, B. R.: Assessment of intraocular pressure in vitrectomized gas-containing eyes. A clinical and manometric comparison of the Tono-Pen to the pneumotonometer. Arch. Ophthalmol. 108:684, 1990.

8. Moses, R. A., and Becker, B.: Clinical tonography. The scleral rigidity correction. Am. J. Ophthalmol. 45:196, 1958.

9. Friedenwald, J. S.: Tonometer calibration. An attempt to remove discrepancies found in the 1954 calibration scale for Schiötz tonometers. Trans. Am. Acad. Ophthalmol. Otolaryngol. 61:108, 1957.

10. McBain, E. H.: Tonometer calibration. Determination of P_t formula by use of strain gauge and recording potentiometer on enucleated normal human eyes. Arch. Ophthalmol. 57:520, 1957.

11. Schmidt, T.: The clinical application of the Goldmann applanation tonometer. Am. J. Ophthalmol. 49:967, 1960.

12. ———: The use of the Goldmann applanation tonometer. Trans. Ophthalmol. Soc. U.K. 79:637, 1959.

13. Saiduzzafar, H.: Studies in ocular rigidity. Br. J. Ophthalmol. 46:717, 1962.

14. Grant, W. M., and Trotter, R. R.: Tonographic measurements in enucleated eyes. Arch. Ophthalmol. 53:191, 1955.

15. Perkins, E. S.: Hand-held applanation tonometer. Br. J. Ophthalmol. 49:591, 1965.

16. Hessemer, V., Rössler, R., and Jacobi, K. W.: Comparison of intraocular pressure measurements with the Oculab Tono-Pen vs manometry in humans shortly after death. Am. J. Ophthalmol. 105:678, 1988.

17. Moses, R. A., Marg, E., and Oechsli, R.: Evaluation of the basic validity and clinical usefulness of the Mackay-Marg tonometer. Invest. Ophthalmol. 1:78, 1962.

A New Method for Documenting Lens Opacities

I. Adamsons, M.D., K. I. Taylor, C. Enger, M.S.,
H. R. Taylor, M.D.

We tested an anterior segment camera and digital analyzer on 32 eyes of 22 patients to determine whether its measurement of lens opacities correlated with measurements obtained by a standardized clinical grading system. The lenses were graded clinically for nuclear opacity, nuclear color, cortical opacity, and posterior subcapsular opacity. The lenses were then photographed and analyzed with this new device, and the results were compared. The camera system showed good reproducibility. Its results correlated well with the clinical gradings for nuclear opacity (P = .001) and cortical opacity (P = .001) but less well with posterior subcapsular opacity (P = .3), although there were only seven eyes with posterior subcapsular opacities. This camera system could help document and follow up lens opacity with more accuracy and reproducibility than has been previously possible.

CATARACTS have proven to be a difficult entity for clinical study, in part because of the difficulty in devising an accurate and reproducible grading system.[1] Grading systems based on visual acuity[2-4] fail to detect early lens changes and are confounded by the concurrent presence of other ocular abnormalities that may be difficult to detect, particularly if lens opacities are advanced.[5] Grading systems based on clinical impressions[6-11] often have large interobserver and intraobserver variability, which increases as the systems move from crude categorization of lens opacities (for example, mature vs immature) to more sophisticated categorization.[7] Grading systems based on the visualization of a target projected onto the retina will not evaluate opacities outside of the visual axis.[5,12] Grading systems based on photodocumentation[7,11-19] of the lens may reduce variability,[9,17,20] allow multiple independent and objective assessments, and may better detect early lens opacities.

An anterior segment and lens camera system has recently been developed in which retroillumination and slit-lamp (Scheimpflug) photographs of the lens are taken and digitized. These digitized photographs are available for on-line computer analysis with accessible software. The potential advantages of this system include the standardized method of operation and the ability to detect early lens opacities. We compared this camera system with a clinical system of cataract grading based on photodocumentation, which has proven to be sensitive and reliable.[17-19]

Patients and Methods

Subjects were selected from patients examined in a general ophthalmology practice during a two-week period. Twenty patients with lens opacities and two patients with clear lenses were entered into the study. Each lens was evaluated through a pharmacologically dilated pupil by a single observer. Based on our standardized method, the lens was graded for the amount of nuclear opacity, cortical opacity, and posterior subcapsular opacity.[17-19,21] Briefly, nuclear opacities and nuclear color were graded by comparison to a set of standard slit-lamp photographs. Cortical opacities were graded in terms of the fraction of the lens circumference occupied as seen on retroillumination. Posterior subcapsular opacities were evaluated in retroillumination by measuring and recording their greatest vertical and horizontal dimensions with the calibration of the slit-beam height.

The second generation anterior segment cam-

Accepted for publication Sept. 25, 1990.

From the Dana Center for Preventive Ophthalmology, Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, Maryland. This study was supported by National Eye Institute grants T32 EY07047 and EY01765.

Reprint requests to I. Adamsons, M.D., 116 Wilmer Bldg., 600 N. Wolfe St., Baltimore, MD 21205.

era incorporated a retroillumination camera and a slit-lamp camera based on the Scheimpflug principle. The camera was on-line with a black and white charge-coupled device digitizing camera and computer monitor. The procedure for taking photographs was automated and required little input from the operator other than aligning the camera. The digitized photographs were displayed on the on-line computer monitor and were stored for analysis. Densitometry and biometry were performed by on-line computer analysis, operator driven with a customized program.

Each patient's lens was graded clinically through a dilated pupil, then photographed with the anterior segment camera system. An independent observer, who was masked to the clinical grading of the lens, evaluated the photographs by following the operator-driven protocol of the system. The slit-lamp photograph was used to identify and measure, in units called points, both the peak nuclear density and the total nuclear density. The total nuclear density was later divided by the total nuclear area, measured in pixels, to obtain the average nuclear density. The retroilluminated photograph was used to determine the opaque area of the lens, which was measured in percentages.

The criteria used were the following: significant nuclear opacities were those graded clinically as 2.0 or greater; significant cortical opacities were those graded clinically as greater than 1/16 of lens circumference; significantly increased peak and average nuclear density were values greater than 70 and 55 points, respectively; and significant opaque areas were values greater than 10%. Eyes with posterior subcapsular opacities were excluded from the analysis of the opaque area because the current computer software could not distinguish cortical from posterior subcapsular opacities.

The reproducibility of the measurements was also evaluated. Two eyes were photographed and measured twice, one week apart, to assess the reproducibility of replicate photographs. Additionally, these eight photographs, four slit-lamp and four retroillumination, were each evaluated ten times by another grader to determine the reproducibility of the computer analysis of a single photograph. The measurements obtained by the two graders were examined for intraobserver and interobserver variability.

Statistical data analysis was performed using SAS for personal computers (SAS Institute, Inc., Cary, North Carolina). Correlations were determined by linear regression techniques. Multiple regression was done to take into account the potential effect of other variables. Nuclear color was evaluated by the Kruskal-Wallis test, a nonparametric analysis of variance.

Results

Of 22 patients, 32 eyes were evaluated clinically, photographed, and analyzed by the computer system. Twenty patients (28 eyes) had nuclear opacities; ten patients (13 eyes) had cortical opacities; and five patients (seven eyes) had posterior subcapsular opacities. Two patients (four eyes) had clear lenses.

To determine the reproducibility of analysis for any single photograph, eight photographs were each evaluated ten times by a single grader. The standard deviation for each set of ten measurements was less than 2.3% of the mean value measured. Comparison of the mean values obtained by the first grader with the values obtained by the second grader showed as high as 38% discrepancy between graders for retroilluminated photographs and as high as 11% discrepancy between graders for slit-lamp photographs.

Peak and average nuclear density correlated with clinically graded nuclear opacity by linear regression analysis ($P = .001$ for both; Figs. 1 and 2). The screening ability of nuclear density measurements demonstrated 92% sensitivity, 94% specificity, and 92% positive predictive values. Opaque area correlated with clinically graded cortical opacity ($P = .001$; Fig. 3) but not with clinically graded posterior subcapsular opacity ($P = .3$; Fig. 4). Since computer analysis of opaque area could not distinguish cortical from posterior subcapsular opacities, lenses with posterior subcapsular opacities were then excluded to determine the accuracy and predictive value of opaque area measurements in screening for cortical opacities. These measurements showed 67% sensitivity, 88% specificity, and 67% positive predictive values.

Since lens opacities are frequently present in various combinations, data were examined for confounding factors by multiple regression analysis. The association between nuclear opacity and nuclear density measurements remained significant regardless of the presence of cortical or posterior subcapsular opacities ($P =$

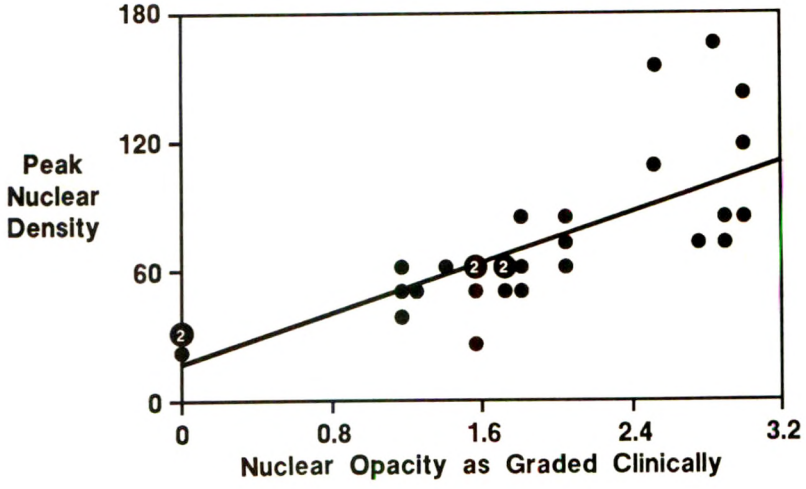


Fig. 1 (Adamsons and associates). The correlation (*r*) of clinically graded nuclear opacities with peak nuclear density ($r = .74$; slope = 30.54; standard error slope = 5.19; $P = .001$).

.001 for all). Additionally, the association of opaque area and cortical opacity was unaffected by the presence of nuclear opacities ($P = .001$). Nuclear color, however, correlated positively with all three computer-generated measurements ($P = .001$ to $P = .04$). Nuclear color also correlated positively with the three clinical lens grades ($P = .001$ to $P = .06$). The association of nuclear color with all three computer-generated measurements, however, was not seen after adjusting for age ($P = .12$ to $P = .31$). This reflects the colinearity between age and nuclear color[22,23] and the strong association between age and cortical and nuclear opacities, and the weaker association with posterior subcapsular opacities.[22,24]

Discussion

This camera system is a highly automated method of photodocumentation and analysis with many advantages. High-quality, slit-lamp photographs[12-14,16] are used for evaluation of nuclear opacities, and retroilluminated photographs are used to document cortical and posterior subcapsular opacities.[15] Camera alignment and focusing is semiautomated, resulting in highly standardized photographs; photographs are displayed immediately so that poor quality ones can be retaken without delay; on-line digitizing eliminates the delay and loss of detail incurred by separate densitometry of

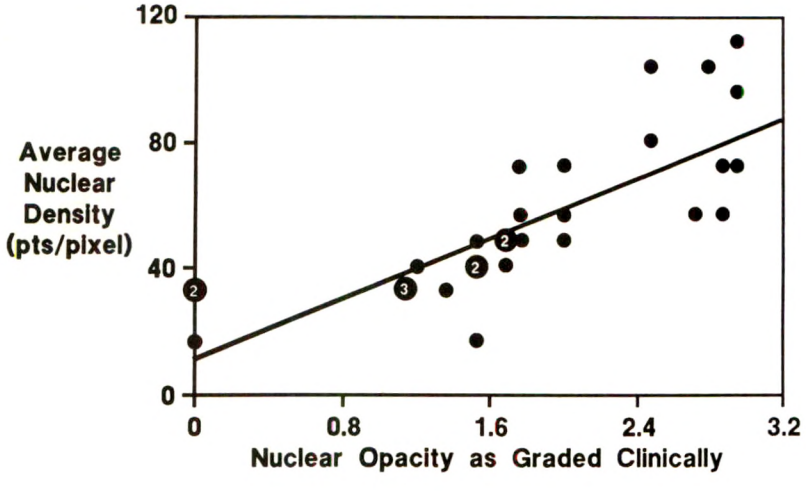


Fig. 2 (Adamsons and associates). The correlation of clinically graded nuclear opacities with average nuclear density ($r = .80$; slope = 23.66; standard error slope = 3.36; $P = .001$).

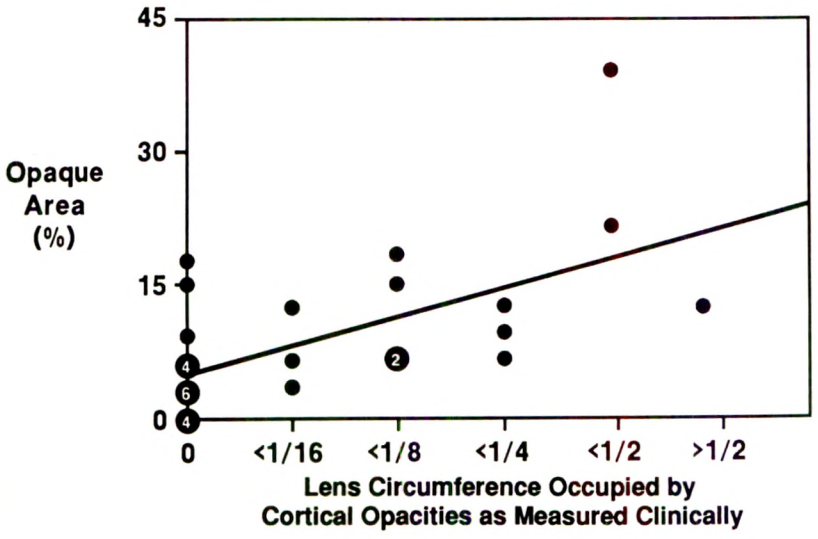


Fig. 3 (Adamsons and associates). The correlation of cortical opacity with opaque lens area (r = .60; slope = 3.24; standard error slope = 0.82; P = .001). The correlation improved when cortical opacity was graded by fraction of lens area occupied rather than of lens circumference (r = .82; slope = 5.20; standard error slope = 0.77; P = .001).

photographs; and the computer analysis requires little subjective operator input, thereby standardizing the photograph measurement.

Repeated analyses, by one person, of any individual photograph were highly reproducible, which suggests that one measurement per grader is adequate. Interobserver reliability was acceptable for slit-lamp photographs but was less so for retroilluminated photographs, indicating that, while analysis of replicate slit-lamp photographs by more than one grader may add to the accuracy of that measurement, analysis of retroilluminated photographs requires improved standardization.

The measurements obtained with this camera system generally correlated well with the clinical measures of opacities. Peak and average nuclear density measurements correlated with clinically graded nuclear opacities and accurately predicted significant nuclear opacity. Opaque area measurements correlated with clinically graded cortical opacities but were less

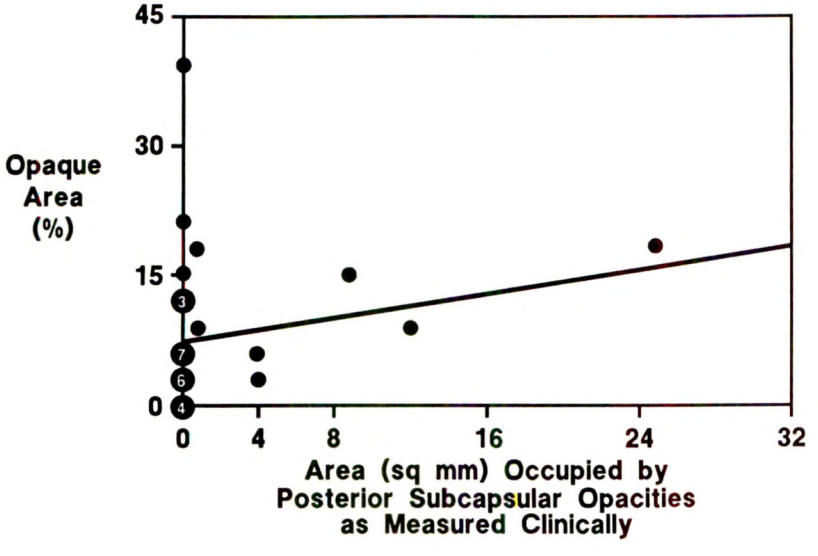


Fig. 4 (Adamsons and associates). The correlation of posterior subcapsular cataracts with opaque area (r = .21; slope = 0.33; standard error slope = 0.29; P = .268).

effective in predicting significant cortical opacity. Opaque area measurements did not correlate with clinically graded posterior subcapsular opacities; however, the study included only a small number of posterior subcapsular opacities. An important drawback of this software is that, during the analysis of retroillumination photographs, one cannot separate between posterior subcapsular and cortical opacities.

The Lens Opacity Meter 701 (Intraoptics, Switzerland) is a clinically available device for documenting lens opacities. Its measurements, however, correlated with clinical lens gradings for nuclear opacity only and showed no correlation with grading for either posterior subcapsular opacities or with cortical opacities.[25] Furthermore, there was a large degree of overlap between the severity of the nuclear opacity and the Lens Opacity Meter measurement, which indicates poor specificity of this device.[25] We believe that this camera system is an improvement over the Lens Opacity Meter. Nuclear opacities were measured accurately and predicted; cortical opacities were measured accurately but predicted less well. Improvements in the system's software that will permit separation of cortical from posterior subcapsular opacities and that will further standardize their evaluation should improve performance with these opacities as well.

ACKNOWLEDGMENT

Kazuyuki Sasaki, M.D., Kanazawa Medical University, Japan, contributed the camera system for this study.

References

1. Sommer, A.: Cataracts as an epidemiologic problem. Am. J. Ophthalmol. 83:334, 1977.

2. Kornzweig, A. L., Feldstein, M., and Schneider, J.: The eye in old age. IV. Ocular survey of over one thousand aged persons with special reference to normal and disturbed visual function. Am. J. Ophthalmol. 44:29, 1957.

3. Martinez, G. S., Campbell, A. J., Reinken, J., and Allan, B. C.: Prevalence of ocular disease in a population study of subjects 65 years old and older. Am. J. Ophthalmol. 94:181, 1982.

4. Taylor, H. R.: The environment and the lens. Br. J. Ophthalmol. 64:303, 1980.

5. West, S., Rosenthal, F., Newland, H. S., and Taylor, H. R.: A comparison of methods for typing and grading lens opacities for field surveys. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1985, p. 119.

6. Brilliant, L. B., Grasset, N. C., Pokhrel, R. P., Kolstad, A., Lepkowski, J. M., Brilliant, G. E., Hawks, W. N., and Pararajasegaram, R.: Association among cataract prevalence, sunlight hours, and altitude in the Himalayas. Am. J. Epidemiol. 118:250, 1983.

7. Brilliant, L. B., Lepkowski, J. M., and Musch, D. C.: Reliability of ophthalmic diagnoses in an epidemiology survey. Am. J. Epidemiol. 118:265, 1983.

8. Chatterjee, A., Milton, R. C., and Thyle, S.: Prevalence and etiology of cataract in Punjab. Br. J. Ophthalmol. 66:35, 1982.

9. Chylack, L. T., White, O., and Tung, W. H.: Classification of human senile cataractous change by the American Cooperative Cataract Research Group (CCRG) method. II. Staged simplification of cataract classification. Invest. Ophthalmol. Vis. Sci. 25:166, 1984.

10. Leibowitz, H. M., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H. A., Nickerson, R. J., Pool, J., Colton, T., Ganley, J. P., Loewenstein, J. I., and Dawber, T. R.: The Framingham Eye Study monograph. An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. Surv. Ophthalmol. 24:335, 1980.

11. Maclean, H., and Taylor, C. J.: An objective staging for cortical cataract in vivo aided by pattern-analyzing computer. Exp. Eye Res. 33:597, 1981.

12. Cotlier, E., Fagadau, W., and Cicchetti, D. V.: Methods for evaluation of medical therapy of senile and diabetic cataracts. Trans. Ophthalmol. Soc. U.K. 102:416, 1982.

13. Hockwin, O., Dragomirescu, V., and Koch, H.-R.: Photographic documentation of disturbances of the lens transparency during aging with a Scheimpflug camera system. Ophthalmic Res. 2:405, 1979.

14. Hockwin, O., Dragomirescu, V., and Laser, H.: Measurement of lens transparency or its disturbances by densitometric image analysis of Scheimpflug photographs. Graefes Arch. Clin. Exp. Ophthalmol. 219:255, 1982.

15. Kawara, T., and Obazawa, H.: A new method for retroillumination photography of cataractous lens opacities. Am. J. Ophthalmol. 90:186, 1980.

16. Sasaki, K.: A new approach to crystalline lens documentation. J. Ophthalmol. Photography 9:112, 1986.

17. Taylor, H. R., and West, S. K.: A simple system for the clinical grading of lens opacities. Lens Res. 5:175, 1988.

18. ———: The clinical grading of lens opacities. Aust. N.Z. J. Ophthalmol. 17:81, 1989.

19. West, S. K., Rosenthal, F., Newland, H. S., and

Taylor, H. R.: Use of photographic techniques to grade nuclear cataracts. Invest. Ophthalmol. Vis. Sci. 29:73, 1988.

20. West, S. K., and Taylor, H. R.: The detection and grading of cataract. An epidemiologic perspective. Surv. Ophthalmol. 31:175, 1986.

21. Bailey, I. L., Bullimore, M. A., Taylor, H. R., and Wang, F.: Improving clinical grading. Application to lens opacities. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 235.

22. Chylack, L. T., Ransil, B. J., and White, O.: Classification of human senile cataractous change by the American Cooperative Cataract Research Group (CCRG) method. III. The association of nuclear color (sclerosis) with extent of cataract formation, age, and visual acuity. Invest. Ophthalmol. Vis. Sci. 25:174, 1984.

23. Pirie, A.: Color and solubility of the proteins of human cataracts. Invest. Ophthalmol. 7:634, 1968.

24. Hiller, R., Sperduto, R. D., and Ederer, F.: Epidemiologic associations with nuclear, cortical, and posterior subcapsular cataracts. Am. J. Epidemiol. 124:916, 1986.

25. Lee, J. A., and Taylor, H. R.: The lens opacity meter. A method of quantification of lens opacity by measurement of scattering of incident light. Lens Eye Toxicity Res. 7:31, 1990.

OPHTHALMIC MINIATURE

Nobody took any notice of Schnak's infatuation but Darcourt; nobody else saw the special quality in her tagging and hanging. Nobody else saw the lovelight in her eyes.

They were not eyes in which one would look for the lovelight. They were small, pebbly, squinty little eyes. Nor was Schnak a figure upon whom love sat like an accustomed garment; her motion was not graceful, because, in one of Darcourt's Old Ontario phrases, she was as bow-legged as a hog going to war . . .

Robertson Davies, *The Lyre of Orpheus*
New York, Penguin Books, 1988, p. 374

Surgical Management of Oculomotor Nerve Palsy

Irene Gottlob, M.D., Robert A. Catalano, M.D., and Robert D. Reinecke, M.D.

We treated seven patients with unilateral oculomotor nerve palsy by transposition of the insertion of the superior oblique tendon to a point anterior and medial to the insertion of the superior rectus muscle without trochleotomy (Scott procedure). Additionally, large recessions of the lateral rectus muscle of involved eyes and, occasionally, recess/resect procedures of horizontal recti muscles of noninvolved eyes were performed. All patients were followed up between one and eight years. Orthophoria in the primary position was achieved and maintained with one operation in four patients. A fifth patient had only a small residual exotropia. In two patients who had aberrant regeneration of the oculomotor nerve, surgery on horizontal recti muscles of the noninvolved eye improved the eyelid position of the involved eye after three operations.

In oculomotor nerve palsy, the eye becomes fixed in a down and out position because of unopposed action of the lateral recti and superior oblique muscles. This position has prompted the development of innovative strabismus procedures aimed at maintaining the eye in the straight-ahead position. The goal of alignment of such eyes in the primary position necessitates acceptance of limited motility of the involved eye. If some residual function of the medial rectus muscle exists, the eyes may be aligned in primary position with a large recession of the lateral rectus muscle combined with a resection of the medial rectus muscle.[1,2] Large resections of a completely paralytic muscle, however, accomplish little. The eye may become exotropic again with time as the lateral rectus muscle undergoes chronic contraction and the resected muscle elongates. If the medial rectus muscle lacks any function, transposition of the superior oblique muscle is usually necessary to exert a tonic adducting force to the globe.

The technique of fracturing the trochlea and attaching the shortened superior oblique tendon to the medial rectus muscle insertion has been recommended by several authors.[3-8] Described initially by Peter[2] and then by Jackson,[3] this procedure is technically difficult and may result in the superior oblique tendon being severed inadvertently at the trochlea, especially in an adult patient with a calcified trochlea. To avoid these difficulties, Scott[9] devised an alternative technique of transposition of the superior oblique tendon without trochleotomy. In the Scott procedure, the superior oblique muscle is first tenotomized at the medial border of the superior rectus muscle. The tendon is sutured to the sclera 2.0 to 3.0 mm anterior to the medial side of the superior rectus muscle insertion. Using this technique, Scott achieved good results in one patient with a congenital oculomotor nerve palsy. Harley,[1] however, observed that less adduction is achieved by this procedure than with the procedures of Peter and Jackson. Saunders and Rogers[10] obtained unsatisfactory results with the Scott procedure in four eyes of three patients with oculomotor nerve palsy. Postoperatively, they reported inadequate horizontal alignment, hypertropias, or paradoxic ocular movements. In contrast, Maruo, Kubota, and Iwashige[11] obtained satisfactory results by transposing the superior oblique tendon without trochleotomy when combined with recession of the lateral and superior recti muscles.

Treatment of the blepharoptosis in some patients has also posed a problem, since a frontalis suspension for a nonmoving eye may cause

Accepted for publication Sept. 11, 1990.

From the Foerderer Eye Movement Center for Children (Drs. Gottlob and Reinecke) and Pediatric Ophthalmology Service (Dr. Reinecke), Wills Eye Hospital, Philadelphia, Pennsylvania; Department of Ophthalmology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania (Dr. Reinecke); and Department of Ophthalmology, Albany Medical College, Albany, New York (Dr. Catalano). This study was supported by an unrestricted grant from Research to Prevent Blindness, Inc., and a grant from the Max Kade Foundation.

Reprint requests to Robert D. Reinecke, M.D., Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

corneal exposure. de Decker[12] described improvement of a blepharoptotic eyelid associated with a oculomotor nerve palsy by surgery on the noninvolved eye. This patient had aberrant regeneration of the oculomotor nerve with eyelid elevation on attempted adduction of the paretic eye. Moving the horizontal recti muscles of the noninvolved eye by a modified Kestenbaum reposition operation caused the fixing eye to have innervation of constant abduction, thereby keeping the eyelid of the affected eye raised. Such repositioning of the noninvolved eye stimulated the lateral rectus muscle of the affected eye. According to Hering's law, the medial rectus muscle of the eye with the oculomotor nerve palsy is also stimulated. Because of aberrant innervation, the eyelid of the involved eye raises while the eyes are in primary position.

We treated seven patients with unilateral oculomotor nerve palsy who underwent transposition of the superior oblique tendon without trochleotomy to a position 2.0 or 3.0 mm anterior to the medial end of the superior rectus muscle insertion (Scott procedure). In the involved eyes of the patients, large recessions of lateral recti muscles were performed. In four patients, these recessions were combined with resections of the medial recti muscles. Additionally, we treated two patients with aberrant regeneration of the oculomotor nerve to the eyelid who underwent a recess/resect procedure of the horizontal recti muscles in the unaffected eye in an effort to raise the affected blepharoptotic eyelid.

Patients and Methods

We reviewed the postoperative eye positions of all patients treated for oculomotor nerve palsy by one of us (R.D.R.) with the Scott procedure between 1979 and 1990. Four patients had congenital oculomotor nerve palsy and three patients had oculomotor nerve palsy after trauma. Two of the seven patients had had previous surgery on horizontal recti muscles. Preoperative ocular motility examination included prism cover measurements and an analysis of the ocular ductions. No patient demonstrated clinically apparent medial rectus muscle function. The function of the superior oblique muscle of the paralytic eye was established by observing an intorsion on attempted downward gaze. The function of the lateral rectus muscle was ascertained by observing a small sluggish medial drift of the eye on attempted adduction, a brisk lateral movement on attempted abduction, and a positive force generation test. All seven patients had functioning superior oblique and lateral recti muscles. In five of the seven patients, ocular movements were recorded by electro-oculography or the magnetic search coil technique. Ocular movement recordings confirmed clinical findings of no residual function of the medial rectus muscle and intact function of the lateral rectus muscle. All patients had blepharoptosis in the involved eyes, and the blepharoptosis was corrected in most of the patients subsequent to ocular muscle surgery.

Surgery was performed on patients while under general anesthesia. Forced duction tests were noncontributory before surgery in six of the seven patients. Limbal incisions were used for all procedures, and the muscles were placed on a Berens' clamp and reattached to the globe with 6-0 Tycron sutures in a figure-eight pattern.[13] The superior oblique muscle was approached through the same incision as the medial rectus muscle and was isolated medial to the superior rectus muscle. According to the technique described by Scott,[9] a 6-0 Tycron suture was passed through the superior oblique tendon at a point that gave some tonic elevation and adduction force in the primary position. The tendon was reattached to the globe 2.0 to 3.0 mm anterior to the medial end of the superior rectus muscle insertion.

The goal of surgery was to align the eyes within 10 prism diopters of orthophoria in primary position. If this was not achieved after the first surgical session, additional procedures were performed. The period of follow-up after the last operation ranged between one and eight years (mean, 3.14 years).

Results

The eyes of three patients (Cases 1, 2, and 3) were orthophoric in the primary position after the first operation. For each of these patients a 14.0-mm or greater recession of the lateral rectus muscle and a 4.0- to 6.0-mm resection of the medial rectus muscle was performed in addition to the Scott procedure. The ocular position of these patients has remained stable during a follow-up period of two to eight years.

In Case 4, the patient had two previous oper-

ations on the right eye and one previous operation on the left eye. Before our first surgery, a marked restriction of adduction and depression of the right eye was found on forced duction testing. Multiple adhesions between the connective tissues and the superior and lateral recti muscles were encountered during surgery. At surgery, both muscles were disinserted and the Scott procedure was performed. After surgery, the patient had a residual right exotropia of 10 prism diopters, which remained stable one year postoperatively.

Preoperatively, the patient in Case 5 had a left exotropia of 60 prism diopters, a left hypotropia of 20 prism diopters, and blepharoptosis of the left upper eyelid (Fig. 1, left). In the left eye, the lateral rectus muscle was recessed 10.0 mm and the Scott procedure was performed; in the right eye, the lateral rectus muscle was recessed 7.0 mm and the medial rectus muscle was resected 5.0 mm. Postoperatively, there was no vertical deviation in primary position; however, the patient had a residual left exotropia of 40 prism diopters. The left lateral rectus muscle was subsequently further recessed 5.0 mm, the left medial rectus muscle was resected 7.0 mm, and the left superior oblique muscle was advanced 5.0 mm. After the second operation, the patient had a consecutive left esotropia of 15 prism diopters. The right lateral rectus muscle was then advanced 4.0 mm, and a frontalis suspension of the left upper eyelid was performed. Orthophoria in the primary position was achieved (Fig. 1, right).

The patient in Case 6, who sustained a traumatic right oculomotor nerve palsy, had a right exotropia of 120 prism diopters preoperatively. The right eye extorted approximately 20 degrees on attempted upgaze, which demonstrated function of the right inferior oblique muscle. This patient had marked aberrant regeneration of the oculomotor nerve. In primary position (Fig. 2, top left), right gaze (Fig. 2, top right), and upgaze (Fig. 2, middle left), an almost complete right blepharoptosis was noted. The right upper eyelid was elevated on attempted left gaze (Fig. 2, middle right) as well as on attempted downward gaze (Fig. 2, bottom left). The right lateral rectus muscle was recessed 16.0 mm, and the Scott procedure was performed on the right superior oblique muscle. To diminish the extortion of this eye on upgaze, the right inferior oblique muscle was disinserted. Additionally, the left medial rectus muscle was resected 5.0 mm, and the left lateral rectus muscle was recessed 10.0 mm. Surgery on the left eye was performed to reduce the exotropia and to improve the position of the eyelid in primary position. After this procedure, the right upper eyelid opened approximately 6.0 mm in primary position, similar to its position during attempted left gaze preoperatively. The patient, however, had a residual right exotropia of 25 prism diopters and a right hypotropia of 15 prism diopters. The right superior oblique muscle was then advanced an additional 3.5 mm, and a levator resection of 12.0 mm was performed on the right upper eyelid. Postoperatively, the patient had a residual right exotropia of 18 prism diopters and a right hypotropia of 5 prism diopters. Blepharoptosis in the right upper eyelid was 4.0 mm. Because of aberrant regeneration, on attempted downward gaze the right upper eyelid elevated and the right eye adducted. Subsequently, a 5.5-mm recession of the left inferior rectus muscle and a 6.0-mm resection of the left superior rectus muscle was performed to stimulate adduction of the right eye and elevation of the right upper eyelid. To avoid anterior segment ischemia, the anterior ciliary arteries of both muscles were isolated and were not severed during surgery. Postoperatively, the patient was orthophoric in primary position with only a minimal blepharoptosis of the right upper eyelid. Slight blepharoptosis of the left inferior eyelid was observed as a conse-

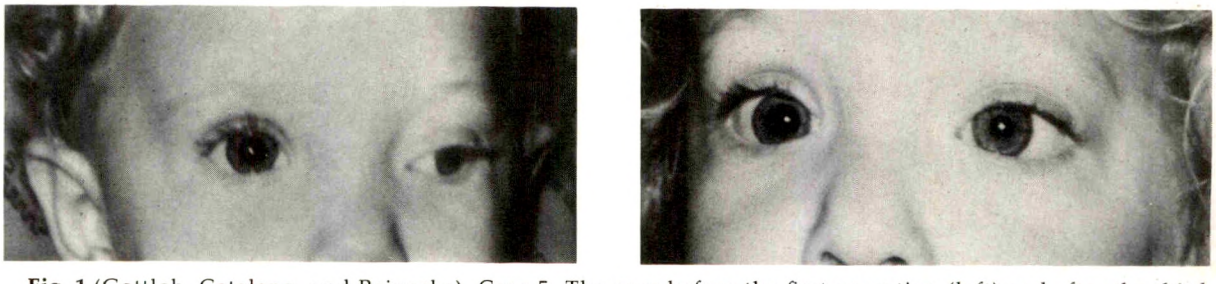


Fig. 1 (Gottlob, Catalano, and Reinecke). Case 5. The eyes before the first operation (left) and after the third operation (right).

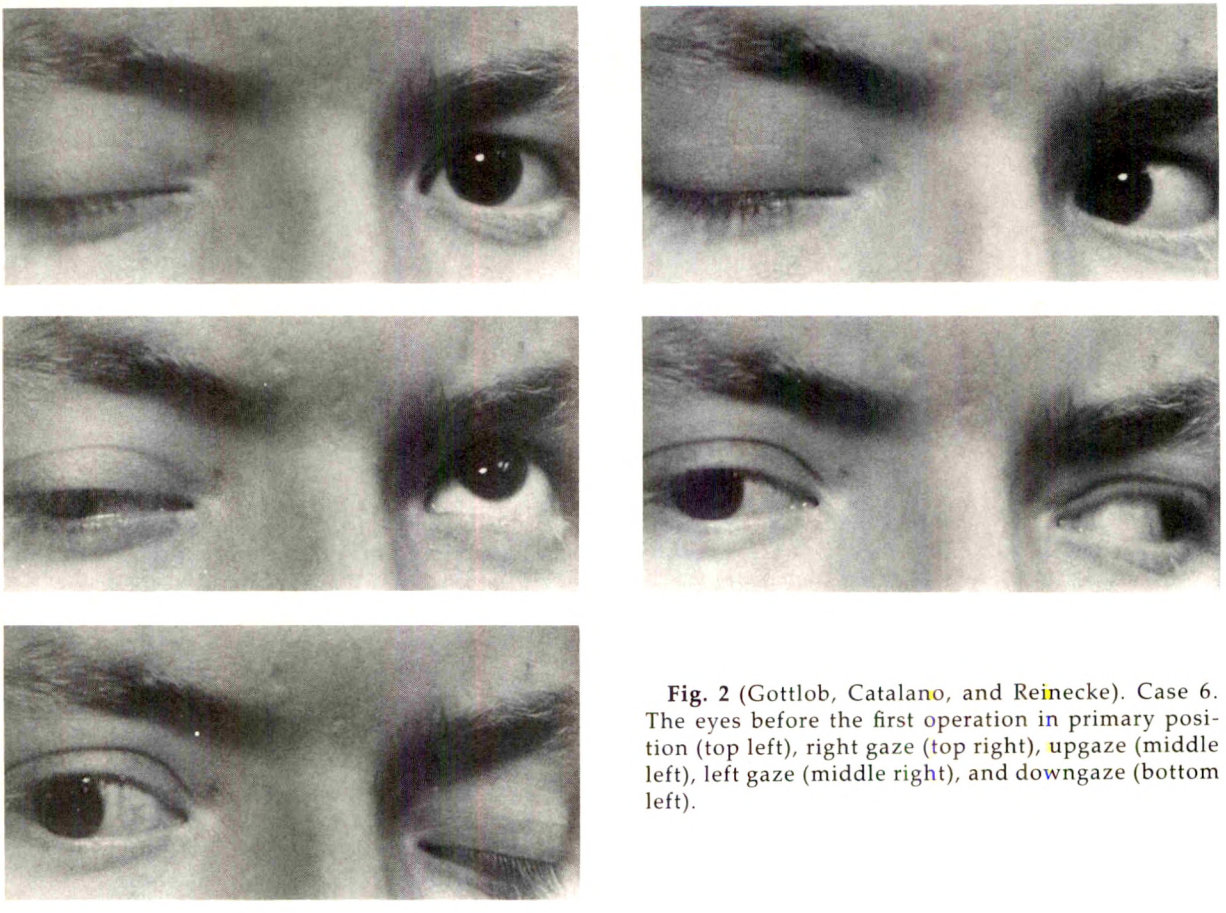


Fig. 2 (Gottlob, Catalano, and Reinecke). Case 6. The eyes before the first operation in primary position (top left), right gaze (top right), upgaze (middle left), left gaze (middle right), and downgaze (bottom left).

quence of the recession of the left inferior rectus muscle. Two years postoperatively, the eyes in primary position were orthophoric, and the patient had mild blepharoptosis of the right upper and the left lower eyelid (Fig. 3).

One patient (Case 7) sustained a traumatic right oculomotor nerve palsy at age 12 years. At age 27 years, the patient had a right exotropia of 60 prism diopters and right hypotropia of 4 prism diopters. On attempted left gaze the right upper eyelid elevated. The right lateral rectus muscle was recessed 8.0 mm, the conjunctiva was recessed laterally 5.0 mm, and the Scott procedure was performed. The left medial rectus muscle was resected 6.0 mm and the left lateral rectus muscle was recessed 9.0 mm on adjustable sutures. The position of the left eye was adjusted after surgery so that the patient was orthophoric in primary position. Similarly, as for the patient in Case 6, the advantage of the aberrant regeneration was taken into consideration in the treatment of this patient. The recess/resect procedure of the horizontal recti muscles of the noninvolved left eye increased innervation of the lateral rectus muscle of this eye and of the contralateral medial rectus muscle in the primary position. The right eyelid was elevated after surgery. Ocular alignment and eyelid position have remained stable over a follow-up period of one year.



Fig. 3 (Gottlob, Catalano, and Reinecke). Case 6. The eyes in primary position after the third operation.

The patients in Cases 2 and 5 had smaller pupils in the involved eyes in some gaze positions, most likely caused by aberrant regeneration. The other patients had symmetric (Cases 1, 3, and 4) or larger, less reactive pupils in the involved eye (Cases 5, 6, and 7).

Discussion

In all of our patients, the Scott procedure combined with recess/resect procedures on recti muscles resulted in a satisfactory cosmetic outcome and alignment in primary position. Orthophoria in the primary position was achieved with one operation in four patients, and one patient had only a small residual exotropia. Two patients needed two additional procedures but were subsequently orthophoric in primary position. These results are comparable with those of patients who underwent the procedures of Peter and Jackson.[3-8] The Scott procedure, however, is technically easier to perform, does not risk severing the superior oblique tendon during trochleotomy, and is reversible.

Our results differ from those of Saunders and Rogers,[10] who obtained inadequate horizontal alignment, hypertropias, or paradoxic ocular movements postoperatively. Different results might be explained by different surgical procedures. Our results suggest that large ipsilateral lateral rectus muscle recession is necessary to achieve alignment. Three patients (Cases 1 through 3), for whom orthophoria in primary position was achieved with one surgery, had a lateral rectus muscle recession of more than 14.0 mm from the original insertion. The good ocular alignment of the patient in Case 7, who underwent only an 8.0-mm recession of the lateral rectus muscle, might be caused by the additional recession of the conjunctiva and by the large recess/resect procedure on the unaffected eye. This compares to the patient in Case 5 who had only a 10.0-mm recession of the lateral rectus muscle and had a residual exotropia of 40 prism diopters after the first surgery. Similarly, Saunders and Rogers[10] treated one patient with bilateral oculomotor nerve palsy with only 11.0-mm recessions of each lateral rectus muscle. This patient had a residual exotropia of 90 prism diopters. Maruo, Kubota, and Iwashige[11] found some correlation between the amount of lateral rectus muscle recession and the amount of correction of exotropia. However, they recessed the lateral rectus muscle in most of their patients only 12.0 mm or less and obtained a residual exotropia of more than 10 prism diopters in 14 of their 20 patients. A second operation with further recession of the lateral rectus muscle decreased the exotropia in five of these patients. Therefore, it appears essential to combine the Scott procedure with a large recession of the ipsilateral lateral rectus muscle of at least 14.0 to 16.0 mm.

In contrast to Saunders and Rogers,[10] we found that none of our seven patients had a cosmetically significant hypertropia after the Scott procedure. Differences might be explained by the different technique of transposing the superior oblique muscle. In all of our patients, the superior oblique muscle was reattached to the sclera where it was shortened only to a point that gave some tonic elevation and adducting force in primary position. Saunders and Rogers[10] may have shortened the superior oblique tendon excessively before resuturing it to the globe. An extremely short and excessively medially placed superior oblique tendon may explain the hypertropias in abduction of the paretic eye of their patients. The purpose of transposing the superior oblique muscle is to prevent a chronic recurrence of the deviation in primary position rather than increase the range of motion of the eye. If no opposing muscle force is present, it is likely that the exotropia will recur. Only a small tonic force is necessary to maintain alignment. Our long-term results, demonstrating stable alignment during a follow-up period of up to eight years postoperatively, confirm that it is not necessary to pull the superior oblique muscle tight to give a leash effect when only a mild adduction force is necessary. Saunders and Rogers[10] found that the eyes of their patients were better aligned after severing the superior oblique tendon. The follow-up period for their patients, however, was not given. Maruo, Kubota, and Iwashige[11] performed additional recessions of the superior recti muscles in their patients. They concluded that the results vertically were not a great deal different in four patients who had no superior rectus muscle recession. This finding is in agreement with our results. In our patients, it was sufficient to eliminate the down-pulling force of the superior oblique muscle by transposition to obtain satisfactory vertical alignment.

Additional surgery on contralateral recti muscles improved the eyelid position in two of

our patients with aberrant regeneration. In these patients (Cases 6 and 7), recess/resect procedures on horizontal recti muscles of the unaffected eyes not only improved the ocular alignment but also raised the affected eyelid in primary position. Both patients had elevation of the eyelid on attempted adduction of the eye with the oculomotor nerve palsy. The noninvolved eyes of these patients were moved toward an adducted position and abducting impulses were, therefore, needed to gaze straight ahead. According to Hering's law, this stimulated nerve fibers to the medial recti muscles of the paralytic eyes that were subsequently innervating the levator muscle. In one patient (Case 6) the affected eye adducted and the eyelid elevated on attempted downward gaze. Surgery of the vertical recti muscles of the noninvolved eye was performed to elevate this eye. Because constant depressing innervation of this eye was needed to hold it in the primary position, consensual impulses to the paretic eye resulted in ocular adduction and eyelid elevation.

We achieved cosmetically satisfactory, long-term results in seven patients with oculomotor nerve palsy without function of the medial rectus muscle by the Scott procedure. Excessive shortening of the superior oblique tendon was not necessary, but orthophoria in primary position required a large recession of the ipsilateral lateral rectus muscle of 14.0 to 16.0 mm. Resection of the medial rectus muscle and recession of the lateral rectus muscle of the noninvolved eye can be added to improve horizontal alignment. In certain cases, Kestenbaum-type surgery on the noninvolved eye of patients with aberrant regeneration may raise the affected blepharoptotic eyelid and help achieve orthophoria in primary position.

References

1. Harley, R. D.: Paralytic strabismus in children. Etiologic incidence and management of the third, fourth and sixth nerve palsies. Ophthalmology 87:24, 1980.

2. Peter, L. C.: The use of the superior oblique as an internal rotator in third-nerve paralysis. Am. J. Ophthalmol. 17:297, 1934.

3. Jackson, E.: Operations on muscles of the eye. In Wiener, M., and Scheie, H. G. (eds.): Surgery of the Eye, ed. 3. New York, Grune and Stratton, 1952, p. 405.

4. Costenbader, F. D.: Round table discussion. In Allen, J. H. (ed.): Strabismus Ophthalmic Symposium II. St. Louis, C. V. Mosby, 1958, p. 502.

5. Helveston, E. M.: Muscle transposition procedures. Surv. Ophthalmol. 16:92, 1971.

6. Reinecke, R. D.: Surgical results of third cranial nerve palsies. N. Y. State J. Med. 72:1255, 1972.

7. Harley, R. D.: Complete tendon transposition for ocular muscle paralysis. Trans. Pac. Coast Otoophthalmol. Soc. 54:81, 1973.

8. Metz, H. S., and Yee, D.: Third nerve palsy. Superior oblique transposition surgery. Ann. Ophthalmol. 5:215, 1973.

9. Scott, A. B.: Transposition of the superior oblique. Am. Orthoptic J. 5:11, 1977.

10. Saunders, R. A., and Rogers, G. L.: Superior oblique transposition for third nerve palsy. Ophthalmology 89:310, 1982.

11. Maruo, T., Kubota, N., and Iwashige, H.: Transposition of the superior oblique tendon for paralytic exotropia in oculomotor palsy. Results in 20 cases. Binoc. Vis. 3:203, 1988.

12. de Decker, W.: The Faden operation. When and how to do it. Trans. Ophthalmol. Soc. U.K. 101:264, 1981.

13. Reinecke, R. D.: Extraocular muscles. In Spaeth, G. L. (ed.): Ophthalmic Surgery. Philadelphia, W. B. Saunders, 1982, pp. 680–682.

Echographic Diagnosis of Dural Carotid-Cavernous Sinus Fistulas

Robert H. Spector, M.D.

I used standardized ophthalmic echography to identify specific abnormalities in four patients with low-pressure, low-flow dural arteriovenous malformations. In all of the patients, B-scan ultrasonography showed engorgement of the ipsilateral vertical vein. A-scan ultrasonography dynamically imaged rapid blood flow through the superior ophthalmic vein and enlargement of the culpable ocular muscles in patients with restrictive ophthalmopathy. The 30-degree test distinguished between venous engorgement of the optic nerve sheath and apical compression of the optic nerve by enlarged ocular muscles.

CAROTID-CAVERNOUS SINUS FISTULAS result from an arteriovenous communication in the region of the cavernous sinus. They can be classified etiologically as spontaneous or traumatic, hemodynamically as high-flow or low-flow, or angiographically into direct or dural fistulas.[1] The direct high-flow, high-pressure fistulas usually occur after head trauma. Sudden rupture of the main carotid trunk into the surrounding cavernous sinus produces an explosive surge of venous engorgement and hypertension, which results in marked dilation of the cavernous sinus and the venous sinuses that normally drain away from and toward the cavernous sinus. Retrograde drainage anteriorly produces engorgement of the superior ophthalmic vein and its tributaries, as well as an impressive array of ocular findings including proptosis, chemosis, restricted motility, and decreased vision secondary to ischemic optic neuropathy or increased intraocular pressure. The severity of proptosis and the threat to visual sensory and motor function often lead to immediate neuroradiologic intervention, with high-resolution computed tomography, magnetic resonance imaging, and selective and superselective carotid and cerebral angiography.

Another type of carotid-cavernous fistula, often called a dural shunt, occurs spontaneously and represents an anomalous connection between small meningeal branches of the internal or external carotid artery and venous channels of the cavernous sinus. These arteriovenous connections lead to a low-flow, low-pressure fistula that behaves differently both clinically and hemodynamically from the direct carotid fistulas.[2-5] When the small-caliber secondary and tertiary dural branches of the intracavernous portion of the carotid artery or the external carotid artery rupture into the cavernous sinus, there is a less dramatic increase in cavernous sinus and orbital venous pressure. Hence, the symptoms and signs of congestive ophthalmopathy evolve more insidiously, are generally milder, and may persist for longer periods of time without jeopardizing corneal, visual sensory, or motor function.[2-6] Additionally, dural fistulas have a relatively high prevalence of spontaneous resolution, ranging in some series from 10% to 60%.[2,6-9] The potential for spontaneous resolution of dural arteriovenous malformations would appear to favor a conservative approach. Using standardized ophthalmic echography, a noninvasive outpatient diagnostic tool, I observed a number of echographic findings indigenous to low-flow, low-pressure fistulas.

Patients and Methods

Four patients with either angiographically proven or presumed dural carotid-cavernous fistulas were studied with standardized ophthalmic echography. In each patient, the superior ophthalmic vein, vertical or median collateral vein, the four recti muscles, and the optic

Accepted for publication Oct. 4, 1990.
Reprint requests to Robert H. Spector, M.D., Ste. 550, 980 Johnson Ferry Rd., Atlanta, GA 30342.

nerve immediately behind the globe and mid-orbit were either imaged or measured. All the echographic determinations were performed at least three times to ensure reproducibility. The techniques for examining the orbital veins,[10,11] the ocular muscles,[10] and the optic nerves[10-12] have been previously reported. The normal range of anterior and posterior optic nerve measurements is 2.2 to 4.4 mm, and this intraocular difference should not exceed 0.3 mm. The normal range of extraocular muscle measurements includes the following: medial rectus muscle, less than 4.6 mm with the difference between pairs not exceeding 0.4 mm; lateral rectus muscle, less than 3.5 mm with the difference between pairs not exceeding 0.6 mm; inferior rectus muscle, less than 3.1 mm with the difference between pairs not exceeding 0.7 mm; and superior rectus muscle, less than 7.1 mm with the difference between pairs not exceeding 0.8 mm. In two patients, the diagnosis of a carotid-cavernous fistula was confirmed angiographically before standardized ophthalmic echography, and in two patients the diagnosis was confirmed by clinical findings alone.

Case Reports

Case 1

A 44-year-old woman had severe, throbbing left hemicranial headaches followed by redness and proptosis of the left globe. Computed tomographic scans showed left-sided proptosis and enlargement of the ipsilateral superior ophthalmic vein. Cerebral angiography disclosed a dural carotid-cavernous sinus fistula between the meningohypophyseal trunk of the intracavernous internal carotid artery and the cavernous sinus.

Visual acuity, pupils, and visual fields were normal. The right fundus was normal, but the left eye showed overfilling of the retinal veins and mild swelling of the optic disk. Intraocular pressure was R.E.: 13 mm Hg and L.E.: 34 mm Hg. Hertel exophthalmometry measurements were R.E.: 16 mm and L.E.: 23 mm. No bruits were heard over the orbits, cranial vault, or neck vessels. Right eye motility was full. Left eye movements were limited to 80% elevation, 70% depression, 50% adduction, and 60% abduction. Results of forced duction testing were positive in all directions. The left temporal sclera contained several hyperemic and dilated, tortuous episcleral veins. The patient was given

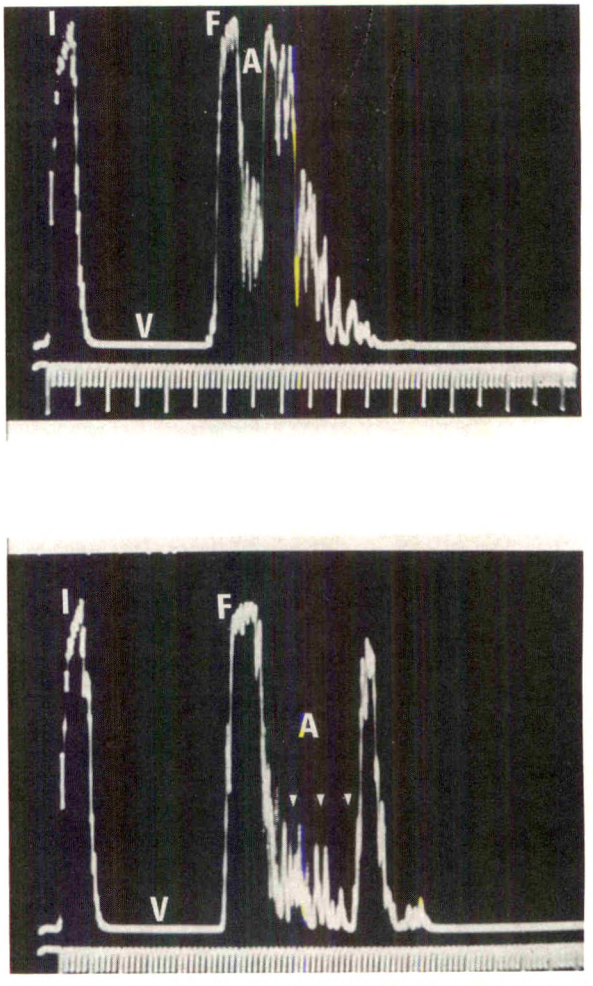


Fig. 1 (Spector). Case 1. Standardized A-scan echograms of an enlarged and arterialized superior ophthalmic vein. The probe is placed behind the corneoscleral limbus at approximately the 7 o'clock meridian with the sound beam aimed through the globe into the superior medial orbit. Top, Echogram obtained from the anterior segment of the enlarged left superior ophthalmic vein. Echolucent area bounded by sharply rising perpendicular spikes outline the superior ophthalmic vein. Bottom, Posterior segment of left superior ophthalmic vein. The venous echogram widens posteriorly, which indicates greater dilation of the superior ophthalmic vein. The low-amplitude, blurred spikes at the base of the echogram represent fast-moving arterialized blood within the superior ophthalmic vein. Initial spike (I) comes from the probe-globe interface at the 7 o'clock meridian behind the corneoscleral limbus. Echolucency in orbital tissue space was caused by enlargement of anterior portion of left superior ophthalmic vein (A). Low-amplitude, blurred spikes resulted from rapid transit of arterialized blood through the superior ophthalmic vein (arrows). (V, clear vitreous; F, fundus signals from retina, choroid, and scleral surfaces.)

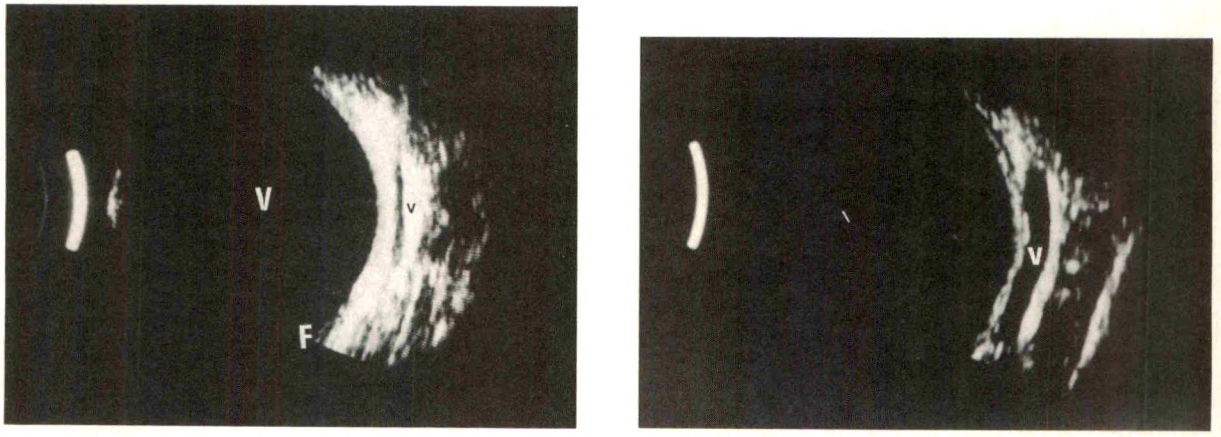


Fig. 2 (Spector). Case 1. Left, Contact B scan of a normal vertical vein. To obtain these images, the B probe was placed vertically along the temporal corneoscleral limbus of the globe and aimed toward the medial rectus muscle. The normal vertical vein echogram is seen as a thin, vertical slither between the medial rectus tendon and the optic nerve. (V, vitreous; F, fundus signals; v, vertical vein.) Right, B-scan echogram of a dilated tortuous vertical vein (v) in an arteriovenous fistula.

levobunolol hydrochloride 0.5% in the left eye twice a day and 250 mg of acetazolamide, four times a day.

Figures 1 and 2 depict the results of A- and B-scan ultrasonography, respectively. A-scan ultrasonography disclosed anterior optic nerve measurements of R.E.: 3.0 mm and L.E.: 3.9 mm; posterior optic nerve measurements of R.E.: 3.1 mm and L.E.: 3.9 mm; and 30-degree optic nerve measurements of 3.2 mm (Fig. 3). Standardized A-scan measurements of the extraocular muscles were the following: right medial rectus muscle, 4.0 mm; left medial rectus muscle, 5.1 mm; right lateral rectus muscle, 3.3 mm; left lateral rectus muscle, 3.8 mm; right inferior rectus muscle, 2.9 mm; left inferior rectus muscle, 3.6 mm; right superior rectus muscle, 6.9 mm; and left superior rectus muscle, 7.6 mm. Over several months, the ocular symptoms and signs resolved fully.

Case 2

A 61-year-old woman had a six-week history of double vision, but she did not have head-

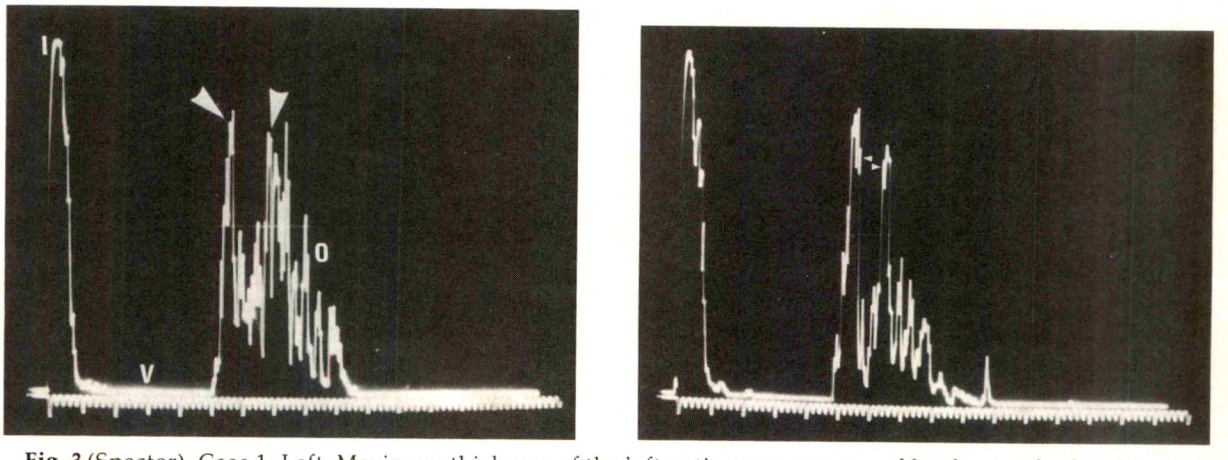


Fig. 3 (Spector). Case 1. Left, Maximum thickness of the left optic nerve, measured by the standardized A-scan method obtained by the transocular method. The left-hand spike represents the probe-eye interface (I), the baseline is vitreous (V), and the echolucent area, bounded on both sides by perpendicular sharply rising spikes, is the optic nerve (enclosed by arrows) (O, normal orbital tissue). Right, Left optic nerve echogram after the left eye was abducted 30 degrees for 30 seconds. Note that the size of the echogram decreased by an amount greater than 10% of the baseline measurement (arrows).

aches, tinnitus, or bruits. The patient had had two coronary artery bypass grafts, an active duodenal ulcer, and a cardiac murmur.

On examination, visual acuity, pupils, color perception, and visual fields were normal. The right fundus was normal, but the left eye showed mild congestion and swelling of the optic disk. The patient had 8 prism diopters of esotropia in primary gaze, 18 prism diopters of esotropia in right gaze, and 14 prism diopters of esotropia in left gaze. Results of forced duction testing were negative. Spiral-shaped, enlarged episcleral vessels were present overlying the insertion of both the medial and lateral recti muscles. A soft, high-pitched systolic bruit was heard around the left globe and the left and right temples. Intraocular pressure was R.E.: 16 mm Hg and L.E.: 21 mm Hg. Hertel exophthalmometry measurements were R.E.: 18 mm and L.E.: 21 mm.

B-scan ultrasonography disclosed dilation of the left superior ophthalmic vein and the left medial collateral vein. A-scan ultrasonography showed a volley of constantly moving low-amplitude spikes at the base of the superior ophthalmic vein echogram. A-scan ultrasonography disclosed anterior optic nerve measurements of R.E.: 2.9 mm and L.E.: 4.4 mm; posterior optic nerve measurements of R.E.: 3.2 mm and L.E. 3.3 mm; and 30-degree optic nerve measurement of 4.2 mm. Measurements of the extraocular muscles were the following: right medial rectus muscle, 4.4 mm; left medial rectus muscle, 4.2 mm; right lateral rectus muscle, 3.5 mm; left lateral rectus muscle, 3.5 mm; right inferior rectus muscle, 3.0 mm; left inferior rectus muscle, 2.9 mm; right superior rectus muscle, 7.0 mm; and left superior rectus muscle, 6.8 mm.

Based on a presumptive diagnosis of a left-sided dural carotid-cavernous sinus fistula, conservative treatment was recommended. The patient returned for follow-up one month later with increased diplopia, and the esotropia was greater than before in both right and left gazes. Results of forced duction testing were again negative. A computed tomographic scan was interpreted as showing an enlarged superior ophthalmic vein on the left side, equivocal enlargement of the right medial rectus muscle and left medial rectus muscle, and the left optic nerve was thickened all along its orbital course. A cerebral angiogram showed a low-pressure, low-flow fistula between the meningohypophyseal branch of the left intracavernous internal carotid artery and the left cavernous sinus. All of the signs resolved in four months.

Case 3

A 69-year-old woman with insulin-dependent diabetes mellitus and a history of allergy to contrast dye had a 12-week history of conjunctivitis in the left eye. Treatment with numerous topical antibiotics was unsuccessful. She was referred for examination after intraocular pressure was found to be asymmetrically increased.

Visual acuity was R.E.: 20/80 and L.E.: 20/60. Pupils and visual fields were normal. Hertel exophthalmometry measurements showed 7 mm of axial, nonpulsatile, left-sided proptosis. Ocular motility disclosed severe limitation of left eye abduction with moderate limitation in other fields of gaze. Results of forced duction testing were negative. Motility of the right eye was normal. Intraocular pressure was R.E.: 10 mm Hg and L.E.: 28 mm Hg. Biomicroscopy disclosed several arterialized episcleral veins temporal to the left corneoscleral limbus. Ophthalmoscopy of the left eye showed congestion of the optic disk, overfilling of the retinal veins, and several small superficial and deep hemorrhages around the posterior pole and midperiphery. Ophthalmodynamometry was not obtained. A soft systolic bruit was heard over the left orbit.

B-scan ultrasonography demonstrated a dilated superior ophthalmic and medial collateral vein in the left eye. A-scan ultrasonography disclosed anterior optic nerve measurements of R.E.: 3.0 mm and L.E.: 4.0 mm; posterior optic nerve measurements of R.E.: 3.1 mm and L.E.: 3.9 mm; and 30-degree optic nerve measurement of 3.0 mm. Measurements of the extraocular muscles were the following: right medial rectus muscle, 4.2 mm; left medial rectus muscle, 5.0 mm; right lateral rectus muscle, 3.0 mm; left lateral rectus muscle, 3.8 mm; right inferior rectus muscle, 3.0 mm; left inferior rectus muscle, 3.9 mm; right superior rectus muscle, 6.3 mm; and left superior rectus muscle, 7.3 mm. Because the clinical and echographic examinations showed strong evidence of a low-flow, low-pressure, carotid-cavernous sinus fistula and also the patient's fragile medical condition and history of contrast dye allergy, further testing was deferred. Over the next eight months, the symptoms and signs resolved spontaneously.

Case 4

An 85-year-old woman developed horizontal diplopia in November 1989, followed one month later by dilated episcleral veins in both eyes, and chemosis. Initially, visual acuity was

20/60 in both eyes. Intraocular pressure was R.E.: 32 mm Hg and L.E.: 31 mm Hg. There was conjunctival swelling and bilateral sixth nerve palsy. A magnetic resonance imaging scan showed a small, right subdural hematoma.

Serial ophthalmologic examinations showed persistent increase and asymmetry of intraocular pressure and presumed sixth nerve palsy. After tortuous, enlarged episcleral vessels became evident, the diagnosis of a dural arteriovenous venous malformation was made. Three years previously, the patient had had two myocardial infarctions three months apart, and one year later she had a minor stroke. The patient also had diabetes mellitus and hypertension.

On examination, visual acuity was R.E.: 20/50 +2 and L.E.: 20/60 +2. Pupils and visual fields were normal. The sclera of each eye had dilated tortuous episcleral veins, but there was no chemosis or bruits heard over the orbits or cranial vault. There was mild bilateral abduction weakness, and results of forced duction testing were negative. The fundus examination of each eye disclosed overfilling of the retinal veins. Intraocular pressure was 18 mm Hg in each eye.

B-scan ultrasonography of the left eye demonstrated mild enlargement of the superior ophthalmic and medial collateral veins. A-scan ultrasonography disclosed anterior optic nerve measurements of R.E.: 3.1 mm and L.E.: 3.0 mm, and posterior optic nerve measurements of R.E.: 3.1 mm and L.E.: 3.0 mm. Measurements of extraocular muscles were the following: right medial rectus muscle, 4.4 mm; left medial rectus muscle, 4.3 mm; right lateral rectus muscle, 3.2 mm; left lateral rectus muscle, 3.4 mm; right inferior rectus muscle, 2.9 mm; left inferior rectus muscle, 3.0 mm; right superior rectus muscle, 6.9 mm; and left superior rectus muscle, 7.0 mm. Ten weeks later, results of an ocular examination were considered normal.

Discussion

Knowledge of the anatomy of the branches of the cavernous internal carotid artery and their anastomoses with neighboring meningeal arteries is the key to an understanding of dural arteriovenous shunts occurring in the region of the cavernous sinus. The ascending internal carotid artery approaches the base of the skull and turns medially, forward, and finally superiorly within the carotid canal to enter the dural envelope formed by the cavernous sinus. The intracavernous portion of the internal carotid artery gives rise to three smaller vessels: the meningohypophyseal artery, the artery of the inferior cavernous sinus, and the capsular artery. Thin-walled, small-caliber secondary and tertiary branches of these vessels lie in the dural membranes that surround the cavernous sinus and supply the adjacent dura mater and cranial nerves. The meningohypophyseal trunk, for instance, branches into the tentorial artery (artery of Bernasconi-Cassonari), the inferior hypophyseal artery, and the dorsal meningeal artery to the clivus. All of these may anastomose within the dura mater of the clivus with ascending secondary and tertiary meningeal branches of the external carotid and vertebral arteries.

All the dural branches of the cavernous internal carotid artery initially pass through or between the sinusoids that comprise the cavernous sinus. When one of these exceedingly small, thin-walled arteries ruptures, a low-flow, low-pressure, carotid-cavernous sinus fistula develops, which produces predictable compensatory changes in the orbital and cavernous sinus venous circulations. The surge of arterial blood into the surrounding venous plexus results in venous engorgement and retrograde blood flow, with dilation of the centrifugal and centripetal veins forming the cavernous sinus. Retrograde blood flow anteriorly, for instance, produces moderate to massive dilation of the superior and inferior ophthalmic veins, with venous stasis in the collateral branches of the superior ophthalmic vein draining the globe, extraocular muscles, and the optic nerves. Venous stasis and hypertension account for the array of clinical findings in these patients, including prominent episcleral veins, proptosis, chemosis, increased intraocular pressure, and vascular engorgement of the retinal veins, optic disks, extraocular muscles, and the optic nerve sheaths. Because of the rich interconnections between the right and left cavernous sinuses, these ocular findings may be seen bilateral, ipsilateral, or contralateral to the actual carotid-cavernous sinus fistula.

Documentation of the anomalous interconnection between these small caliber vessels and the cavernous sinus fistulas has traditionally depended upon high-resolution computed tomography, magnetic resonance imaging, or both, with complete and selective cerebral angiography. Computed tomography and magnetic resonance imaging capably depict the secondary changes of congestive ophthalmopathy, the proptosis, enlargement of the superior

ophthalmic vein, and engorgement of the extraocular muscles. Selective and superselective cerebral angiography displays the bulbous enlargement of the cavernous sinus and draining veins and dynamically images the anomalous interconnections between branches of the internal carotid artery, the external carotid artery, and the cavernous sinus.

In recent years, standardized ophthalmic echography has been used to depict the size and shape of a number of orbital structures, including the orbital veins, extraocular muscles, and the optic nerves.[10-12] Standardized echography appeared to be an ideal diagnostic tool for these lesions, because it images or measures the size of the orbital structures affected by acute or subacute congestive ophthalmopathy. The procedure itself is risk-free, convenient, and relatively inexpensive, and it can be used safely in patients who are old, infirm, or have concomitant medical problems that increase the risks of detailed and prolonged selective cerebral angiography.

Standardized ophthalmic echography provides precise and quantitative data to explain the array of clinical phenomena that occur with low-flow, low-pressure, carotid-cavernous sinus fistulas. For instance, A-mode echography can be used to measure the size of the extraocular muscles precisely, numerically, and repeatedly. This is particularly useful in patients with diplopia in whom forced duction testing gives equivocal results. By measuring the size of the extraocular muscles, the examiner can decide whether the ophthalmoplegia has a restrictive component, since orbital congestion engorges and enlarges the extraocular muscles.

B-scan ultrasonography shows the engorgement of the ethmoidal, superior, and vertical ophthalmic veins better than computed tomography or magnetic resonance imaging. To appreciate this application of standardized ophthalmic echography fully, certain anatomic features of the orbital venous system should be reviewed (Fig. 4). After traversing the superior orbital fissure, the superior ophthalmic vein courses diagonally from a posterolateral to an anteromedial position above the optic nerve. Midway in the orbit, between the optic nerve and the anterior portion of the medial rectus muscle, it anastomoses with the inferior ophthalmic vein through the vertical or median collateral vein. The vertical vein can be identified echographically, even in normal cases.

To display the vertical vein echographically with the B probe, it is necessary to obtain a vertical transverse section of the medial rectus muscle tendon first. After the insertion of the tendon is identified, the probe is angled posteriorly until the anterior portion of the optic nerve is seen. The vertical vein lies in the vertical echographic plane between the optic nerve and the medial rectus muscle. By tilting the top end of the probe posteriorly and the inferior end anteriorly, the vertical vein becomes visible as a thin, dark line. With engorgement of the vertical vein, as in a carotid-cavernous fistula, dilation of the vertical vein becomes echographically obvious (Fig. 2, right).

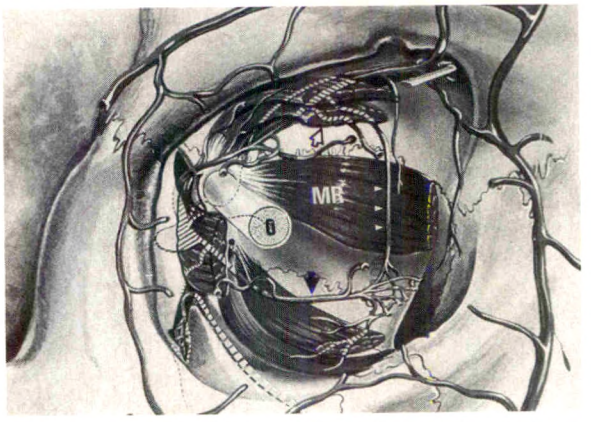


Fig. 4 (Spector). Major orbital veins, right eye. The connecting or vertical vein (arrowheads) connects the superior (open arrow) and the inferior (black arrow) ophthalmic veins. Note the anatomic position of the vertical vein between the medial rectus muscle (MR) and the optic nerve (O).

The actual size of the superior ophthalmic and medial collateral veins can be determined with the A probe (Fig. 1). First, the anterior medial rectus muscle is identified. As the probe and sound beam are angled posteriorly, a small, well-outlined depression becomes visible to the left of the medial rectus pattern (Fig. 1, top). Further posteriorly, the examiner may observe a volley of fast-moving, low-amplitude spikes within the envelope of the superior ophthalmic vein, representing the effects of rapidly flowing blood (Fig. 1, bottom). A- and B-scan ultrasonography can be used together to image the angular and the anterior ethmoidal veins, both of which may be engorged with carotid-cavernous sinus fistulas. These appear as multiple, small, echolucent areas with B scan and as low-to-medium reflective cavernous spaces behind the medial canthus with the A scan.

Two patients (Cases 1 and 3) underwent computed tomography, which reportedly showed

enlargement of the superior ophthalmic vein only. No interpretation was offered regarding the size of the extraocular muscles or the optic nerves. Hence, ophthalmoparesis was mistakenly attributed to cranial nerve dysfunction when the clinical and echographic findings clearly indicated a restrictive ophthalmopathy.

Standardized echography determined whether the optic disk edema in these patients was caused by apical compression of the optic nerve by enlarged extraocular muscles (Cases 1 and 3) or by retinal venous engorgement (Case 2). The 30-degree test was used for this purpose. It is performed by measuring the size of the optic nerve echogram with the eye in primary position and after abduction of the ipsilateral globe 30 degrees. If the size of the optic nerve echogram decreases by more than 10% after 30 degrees of abduction, the optic nerve enlargement can be attributed to distention of the subarachnoid space by cerebrospinal fluid. This occurs with papilledema from increased intracranial pressure and partial apical compression of the optic nerve from a mass lesion or enlarged extraocular muscle. Moving the globe into eccentric horizontal gaze presumably squeezes the spinal fluid out of the subarachnoid space by tethering the vaginal sheaths. Two patients (Cases 1 and 3) had a positive 30-degree test, proving there was pooling of subarachnoid fluid anteriorly, secondary to partial compression of the apical optic nerve sheath. The patient described in Case 2 had clinical signs of a plethoric optic disk ipsilateral to the carotid-cavernous sinus fistula, but the 30-degree test showed that the size of the echogram did not change appreciably after eccentric gaze. The optic nerve swelling could be attributed to venous engorgement of the optic nerve sheath rather than apical nerve compression, a conclusion supported by the observation that the diplopia did not result from ocular muscle engorgement but from sixth nerve dysfunction. Enlargement of the optic nerve sheath associated with venous obstructive retinopathy has been reported.[14]

Considering the relatively optimistic prognosis of low-pressure, low-flow dural arteriovenous malformations, the initial approach to confirming the diagnosis should be deliberate. The present study clearly emphasizes the technical advantages of standardized ophthalmic echography as well as the convenience, savings, and safety of performing this study in an outpatient setting. Unless the conditions warrant therapeutic intervention, standardized ophthalmic echography can be used alone to confirm the diagnosis of a dural carotid-cavernous sinus fistula.

References

1. Barrow, D. L., Spector, R. H., Braun, I. F., Landman, J. A., Tindall, S. C., and Tindall, G. T.: Classification and treatment of spontaneous carotid cavernous fistulas. J. Neurosurg. 62:248, 1985.
2. Newton, T. H., and Hoyt, W. F.: Dural arteriovenous shunts in the region of the cavernous sinus. Neuroradiology 1:71, 1970.
3. Leonard, T., Mosely, I., and Sanders, M. D.: Ophthalmoplegia in carotid cavernous sinus fistula. Br. J. Ophthalmol. 68:128, 1984.
4. Phelps, C. D., Thompson, H. S., and Ossoinig, K. C.: The diagnosis and prognosis of atypical carotid-cavernous fistula (red-eyed shunt syndrome). Am. J. Ophthalmol. 93:423, 1982.
5. Grove, A. S., Jr.: The dural shunt syndrome. Pathophysiology and clinical course. Ophthalmology 91:31, 1984.
6. de Keizer, R. J. W.: Spontaneous carotid-cavernous fistulas. The importance of the typical limbal vascular loops for the diagnosis, the recognition of glaucoma and the uses of conservative therapy in this condition. Doc. Ophthalmol. 46:403, 1979.
7. Ossoinig, K. C., Frieling, E., Tamburrelli, C., and Warner, L.: Superior ophthalmic vein thrombosis. An echographic diagnosis. In Ossoinig, K. C. (ed.): Ophthalmic Echography. The Netherlands, Martinus Nijhoff, 1987, pp. 527–537.
8. Ossoinig, K. C., Cennamo, G., and Frazier-Byrne, S.: Echographic differential diagnosis of optic nerve lesions. Doc. Ophthalmol. 29:327, 1981.
9. Gans, M. S., Frazier-Byrne, S., and Glaser, J. S.: Standardized A-scan echography in optic nerve disease. Arch. Ophthalmol. 105:1232, 1987.
10. Parkinson, D.: Collateral circulation of the cavernous carotid artery. Can. J. Surg. 7:251, 1964.
11. de Keizer, R. J. W.: Spontaneous carotid-cavernous fistulas. Neuro-ophthalmology 2:35, 1981.
12. Peeters, F. L. M., and Kroger, R.: Dural and direct cavernous sinus fistulas. AJR 132:599, 1979.
13. Raskind, R., Johnson, N., and Hance, D.: Carotid cavernous fistula in pregnancy. Angiology 28:671, 1977.
14. Taniguchi, R. M., Goree, J. A., and Odom, G. L.: Spontaneous carotid-cavernous shunts presenting diagnostic problems. J. Neurosurg. 35:384, 1971.
15. Hupp, A. L., Buckley, E. G., Byrne, S. F., Tenzel, R. R., Glaser, J. S., and Schatz, N. S.: Posttraumatic venous obstructive retinopathy associated with enlarged optic nerve sheath. Arch. Ophthalmol. 102:254, 1984.

Human and Monkey Corneal Endothelium Expression of Low-Density Lipoprotein Receptors

Susan G. Elner, M.D., Victor M. Elner, M.D., Mark A. Pavilack, M.D., Harry R. Davis, Ph.D., Joseph A. Cornicelli, Ph.D., and Beatrice Y. J. T. Yue, Ph.D.

Receptors for low-density lipoprotein are necessary for high-affinity uptake of lipid and protein essential to cell structure and function. Distinct receptors for acetoacetylated low-density lipoprotein internalize oxidized or enzymatically modified low-density lipoprotein and extracellular matrix components. We identified low-density lipoprotein receptors on cultured human and monkey corneal endothelial cells by the avid incorporation of fluorescently labeled low-density lipoprotein that was competitively inhibited by excess unlabeled low-density lipoprotein but not by unlabeled acetoacetylated low-density lipoprotein. Specific uptake of labeled low-density lipoprotein was greatest in nonconfluent, growing cells and increased after low-density lipoprotein deprivation. Intact endothelial monolayers of whole human corneas also incorporated low-density lipoprotein but not acetoacetylated low-density lipoprotein. After scratch injury of human corneas, spreading endothelium adjacent to areas of cell loss internalized more fluorescent low-density lipoprotein than cells distant from the injury. Blood-aqueous barrier breakdown occurring in ocular diseases and after surgical and nonsurgical trauma may allow leakage of circulating low-density lipoprotein, which provides a rich supply of lipid and protein for endothelial use. Efficient, receptor-mediated, low-density lipoprotein uptake may facilitate repair of damaged corneal endothelial membranes and regeneration of intact, functional cell monolayers.

Accepted for publication Sept. 19, 1990.

From the Departments of Ophthalmology, Kellogg Eye Center (Drs. S. Elner, V. Elner, and Pavilack) and Pathology (Dr. V. Elner), University of Michigan, Ann Arbor, Michigan; Department of Pathology, University of Chicago, Chicago, Illinois (Dr. Davis); Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan (Dr. Cornicelli); and Department of Ophthalmology, University of Illinois, Chicago, Illinois (Dr. Yue). This study was supported in part by grants EY07003, EY03890, EY07038, and EY01792 from the National Institutes of Health.

Reprint requests to Victor M. Elner, M.D., Kellogg Eye Center, University of Michigan, 1000 Wall St., Ann Arbor, MI 48105.

THE ENDOTHELIAL MONOLAYER on the posterior corneal surface is essential to corneal homeostasis. Mature corneal endothelial cells, especially those in primates, have limited potential for replication.[1-3] After injury, the primate corneal endothelial monolayer is repaired primarily through migration and enlargement of the remaining endothelial cells.[1-3] Aging and a variety of pathologic conditions reduce the total numbers of endothelial cells on human corneas.[4] Similar to that of other cell types, the ability of compromised corneal endothelial cells to maintain their integrity may rely on efficient incorporation of protein and lipid through high-affinity receptors.

In tissue, low-density lipoprotein receptors bind the protein constituents of low-density lipoprotein, namely apolipoproteins B and E, to mediate the endocytosis of cholesterol-rich low-density lipoprotein.[5] Once internalized, low-density lipoprotein is hydrolyzed to produce amino acids, fatty acids, and free cholesterol for cellular use.[5] Many cells express only small numbers of low-density lipoprotein receptors in resting states but are able to augment these cell surface receptors with cell growth and increases in cellular cholesterol requirements.[6,7] Receptor-mediated, low-density lipoprotein uptake is required for optimal growth of cultured cells,[8] presumably by providing a fresh supply of cholesterol for the synthesis of cell membranes.[9]

Distinct receptors for modified low-density lipoprotein, also known as scavenger receptors, bind low-density lipoprotein molecules chemically modified at lysine residues by acetoacetylation,[10] acetylation,[11] or by conjugation with

malondialdehyde.[12] Similar modifications of low-density lipoprotein may result from the action of enzymes, such as neutrophil-derived elastase,[13] or from peroxidation.[14] Scavenger receptors are different from those for low-density lipoprotein and are present on macrophages,[11] vascular endothelial cells,[15] and retinal pigment epithelial cells (Victor M. Elner, M.D., unpublished data). These receptors may also internalize modified serum albumin[16] and extracellular matrix components,[17] leading to the degradation of damaged proteins.

We incubated whole human corneas and cultured human and monkey corneal endothelial cells with low-density lipoprotein and acetoacetylated low-density lipoprotein labeled with a red, fluorescent dye. Our aim was to determine whether corneal endothelial cells possess low-density lipoprotein and acetoacetylated low-density lipoprotein receptors and to determine whether low-density lipoprotein receptor activity increases with cell growth and repair after corneal endothelial injury.

Material and Methods

Human corneal endothelium–Descemet's membrane explants were excised from donor eyes of a 2-year-old that were obtained within 24 hours of death from the Illinois Eye Bank. Explants were cultured in Falcon Primaria flasks (Falcon Laboratories, Becton-Dickinson & Company, Lincoln Park, New Jersey) in 10% fetal bovine serum and 5% calf serum (Hazleton Dutchland Incorporated, Lenexa, Kansas) as previously described.[18] Third-passage corneal endothelial cells exhibiting typical polygonal morphologic characteristics were grown to confluence and passaged by standard methods.[18] Human donor corneas of good quality but unsuitable for transplantation were obtained from the Michigan Eye Bank and Transplantation Center and maintained in Dexsol (Chiron Ophthalmics, Irvine, California). Third-passage rhesus monkey corneal endothelial cells were isolated and passaged by established methods.[19] Third-passage rabbit smooth muscle cells grown from aortic explants and freshly prepared rabbit alveolar macrophages were used in control assays. The smooth muscle cells were cultured in Dulbecco's Modified Essential Medium containing 10% fetal bovine serum.

Four to five days before experimental incubations, corneal endothelial and smooth muscle cells were plated into glass slide chambers. Rabbit alveolar macrophages, isolated by pulmonary lavage with lactated Ringer's solution, were seeded into the slide chambers two to six hours before experimental incubations and maintained in Dulbecco's Modified Essential Medium containing 15% fetal bovine serum.

Human and monkey low-density lipoprotein was isolated, acetoacetylated, and labeled as previously described.[20] Low-density lipoprotein and lipoprotein-deficient serum were obtained by sequential density gradient ultracentrifugation from normal plasma. The red, fluorescent dye, 3,3′-dioctadecylindocarbocyanine, was used to label the isolated low-density lipoprotein by the method of Pitas and associates.[21] The fluorescently labeled low-density lipoprotein was reisolated by centrifugation and dialyzed against 0.9% sodium chloride containing 0.01% ethylenediaminetetraacetic acid, pH 7.0, to obtain purified fluorescent low-density lipoprotein or against 0.1 mol/l of borate buffer, pH 8.4, to obtain labeled low-density lipoprotein for acetoacetylation. After acetoacetylation, the fluorescent, modified low-density lipoprotein was purified by dialysis into 0.02 mol/l of carbonate/bicarbonate buffer, pH 9.4. Complete acetoacetylation was confirmed by agarose gel electrophoresis and subsequent fat red 7B staining of the purified native and acetoacetylated low-density lipoprotein.

The cellular uptake of fluorescent low-density lipoprotein and acetoacetylated low-density lipoprotein was examined by the method of Pitas and associates.[21] To examine increased low-density lipoprotein receptor expression after low-density lipoprotein deprivation, some cultures were maintained in Dulbecco's Modified Essential Medium containing 10% lipoprotein-deficient serum for 24 to 48 hours before experimental incubations. Immediately before experimental incubations, all cultures were rinsed in Dulbecco's Modified Essential Medium containing 10% lipoprotein-deficient serum. The corneal endothelial cell, smooth muscle cell, and macrophage cultures were then incubated in Dulbecco's Modified Essential Medium containing 10% lipoprotein-deficient serum and 15 μg/ml of either labeled low-density lipoprotein or acetoacetylated low-density lipoprotein. In some preparations, fucoidin (30 μg/ml), a competitive inhibitor of acetoacetylated low-density lipoprotein binding and uptake,[22] nonfluorescent acetoacetylated low-density lipoprotein (150 μg/ml), or unlabeled low-density lipoprotein (150 μg/ml) was added to cell cultures 15 minutes before and during fluorescent low-density lipoprotein and aceto-

acetylated low-density lipoprotein incubations. After two-hour incubations at either 4 or 37 C, the cells were rinsed with phosphate-buffered saline containing 2 mg/ml of bovine serum albumin, fixed for 20 minutes in 4% paraformaldehyde, and mounted in buffered glycerol. Incubations were performed in triplicate, and all experiments were repeated at least three times. A minimum of 200 cells were counted in each preparation, and the percentage of fluorescently labeled cells reported is the average value rounded to the nearest 5%.

Identical incubations with fluorescent low-density lipoprotein and acetoacetylated low-density lipoprotein with and without competitive inhibitors were performed in duplicate on whole human corneas. To study the effect of injury on receptor-mediated low-density lipoprotein uptake, 2.0-mm linear endothelial defects were created across the diameters of several additional corneas with 18-gauge hypodermic needles 24 hours before lipoprotein incubations. After fixation in 4% paraformaldehyde for 24 hours, 6-μm frozen sections were cut and mounted in buffered glycerol. The endothelial layer lining the entire posterior surface of each corneal section was examined for fluorescence.

Results

Virtually 100% of cultured human and monkey corneal endothelial cells exposed to labeled low-density lipoprotein became brightly fluorescent after preincubation in lipoprotein-deficient media (Figs. 1 and 2). The red fluorescent low-density lipoprotein was distributed in a punctate pattern on the cell surface and throughout the cytoplasm with increased concentration in the perinuclear region. Competitive inhibition by unlabeled low-density lipoprotein markedly reduced fluorescent low-density lipoprotein binding and uptake (Fig. 1). Competition with unlabeled acetoacetylated low-density lipoprotein or fucoidin did not reduce the intensity of corneal endothelial fluorescence upon exposure to labeled low-density lipoprotein. Fluorescent low-density lipoprotein uptake by all of the corneal endothelial cells preincubated in 10% fetal bovine serum resulted in weaker labeling than that obtained in cells maintained in lipoprotein-deficient media.

Nonconfluent areas of the corneal endothelial cultures displayed greater uptake of fluorescent low-density lipoprotein than confluent regions containing polygonal arrays of cells (Figs. 1 and 2). This was particularly evident at the growing edge of the cultures where endothelial cells, frequently possessing pseudopods, exhibited intense fluorescence caused by avid incorporation of labeled low-density lipoprotein. When incubated with labeled acetoacetylated low-density lipoprotein, fewer than 25% of the cultured corneal endothelial cells showed minimal fluorescence, which was only partially reduced by excess unlabeled acetoacetylated, but not native, low-density lipoprotein (Fig. 1).

Fluorescent low-density lipoprotein uptake by corneal endothelial cells in sections of whole human corneas paralleled that seen with cultured cells (Fig. 3). Virtually all of the cells of intact corneal endothelial monolayers internalized fluorescent low-density lipoprotein but only minimal amounts, if any, of acetoacetylated low-density lipoprotein (Fig. 3). Acetoacetylated low-density lipoprotein uptake was clearly visible, however, in perilimbal vascular endothelial cells of the same whole corneas. Competition with unlabeled low-density lipoprotein, but not acetoacetylated low-density lipoprotein, effectively inhibited labeled low-density lipoprotein uptake.

Central endothelial defects were still visible in sections of whole human corneas exposed to lipoproteins 24 hours after scratch injury to their endothelial surfaces (Fig. 3). Incubation with fluorescent low-density lipoprotein after scratch injury resulted in highly intense labeling of the spreading endothelial cells immediately adjacent to the areas of cell loss (Fig. 3). The uptake of low-density lipoprotein was especially intense within 0.5 mm of the central endothelial defects. Progressive reduction in endothelial fluorescence was observed at greater distances. Endothelial cells greater than 1.0 mm from the site of injury exhibited lipoprotein uptake similar to that seen in uninjured monolayers (Fig. 3). Scratch injury did not increase the fluorescent acetoacetylated low-density lipoprotein labeling of endothelial cells from the minimal amount seen in intact monolayers.

Control preparations of cultured rabbit alveolar macrophages and smooth muscle cells confirmed the specificity of the low-density lipoprotein incorporation by corneal endothelial cells.[21] More than 90% of alveolar macrophages exposed to labeled acetoacetylated low-density lipoprotein were brightly fluorescent. Fucoidin and unlabeled acetoacetylated low-density lipoprotein, but not unlabeled low-density lipoprotein, reduced the number of fluorescent

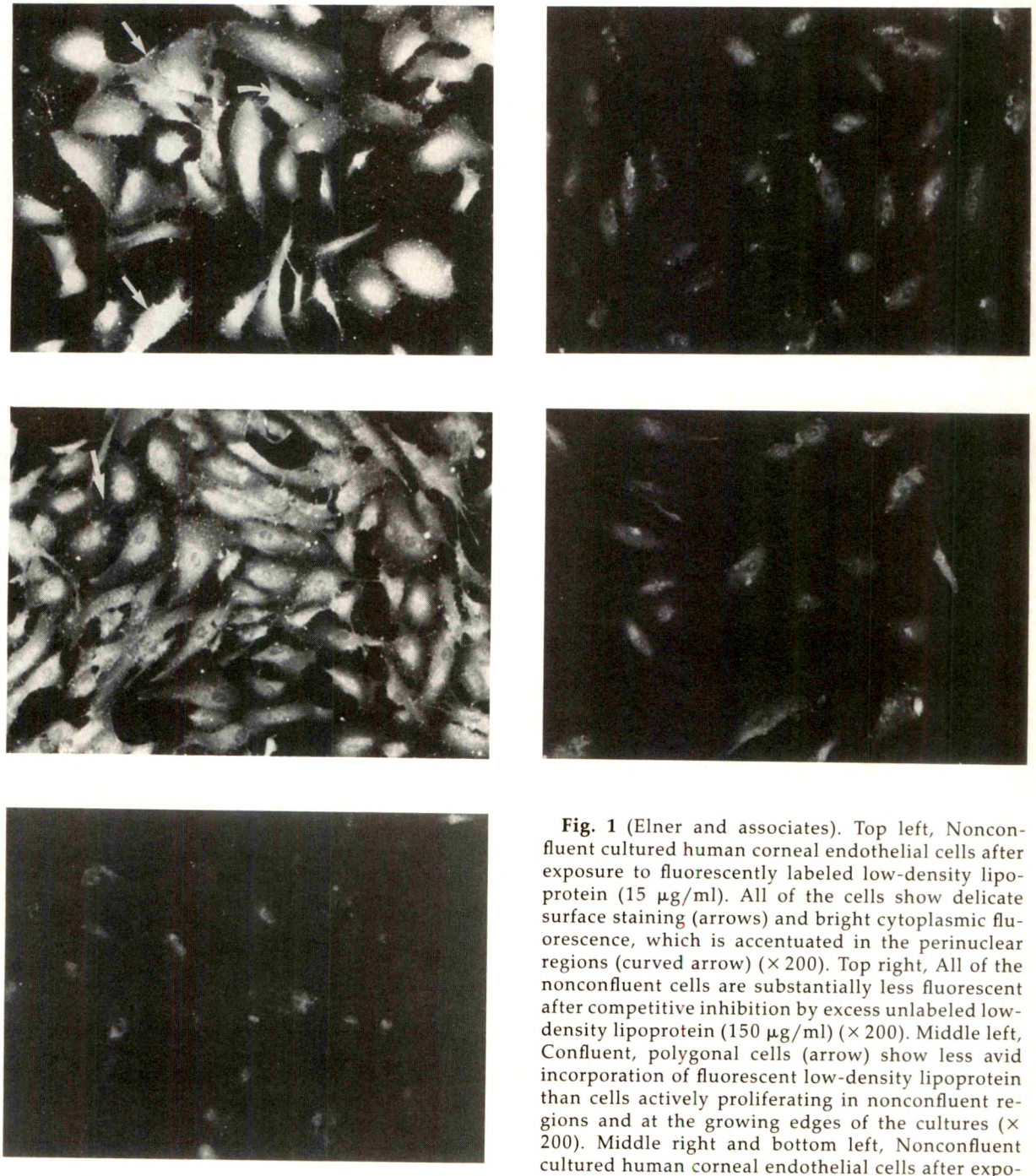


Fig. 1 (Elner and associates). Top left, Nonconfluent cultured human corneal endothelial cells after exposure to fluorescently labeled low-density lipoprotein (15 μg/ml). All of the cells show delicate surface staining (arrows) and bright cytoplasmic fluorescence, which is accentuated in the perinuclear regions (curved arrow) (× 200). Top right, All of the nonconfluent cells are substantially less fluorescent after competitive inhibition by excess unlabeled low-density lipoprotein (150 μg/ml) (× 200). Middle left, Confluent, polygonal cells (arrow) show less avid incorporation of fluorescent low-density lipoprotein than cells actively proliferating in nonconfluent regions and at the growing edges of the cultures (× 200). Middle right and bottom left, Nonconfluent cultured human corneal endothelial cells after exposure to fluorescently labeled acetoacetylated low-density lipoprotein (15 μg/ml). Fewer than 25% of the cells show minimal fluorescence (middle right) (× 200), which is only partially reduced by excess unlabeled acetoacetylated low-density lipoprotein (150 μg/ml) (bottom left) (× 200). Cells not incorporating acetoacetylated low-density lipoprotein are not visible in the fluorescent photomicrographs. Lipoprotein incubations were performed simultaneously. All photomicrographs were taken using the same exposure.

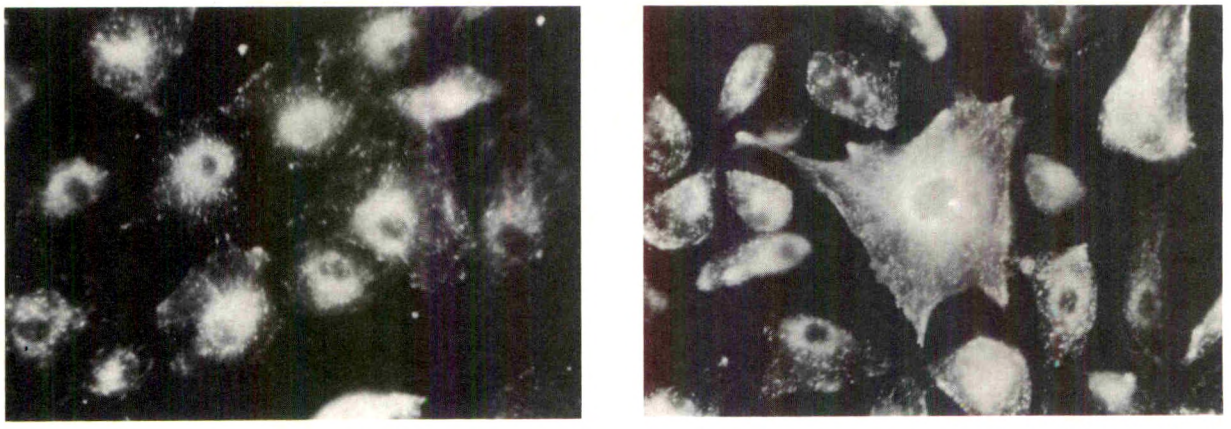


Fig. 2 (Elner and associates). Left, Confluent, polygonal, cultured monkey corneal endothelial cells show punctate surface fluorescence and chiefly perinuclear cytoplasmic fluorescent low-density lipoprotein (× 200). Right, Nonconfluent cells at the growing edge of the same culture show similar, but much more avid, low-density lipoprotein surface binding and cytoplasmic incorporation (× 200).

macrophages to less than 15%. These macrophages were also less fluorescent than macrophages incubated in the absence of inhibitors. Exposure to fluorescent low-density lipoprotein resulted in weak labeling of 10% to 40% of macrophages, which was virtually abolished by excess unlabeled low-density lipoprotein.

Almost 100% of smooth muscle cells preincubated in lipoprotein-deficient media exhibited bright fluorescence when exposed to labeled low-density lipoprotein. The addition of unlabeled low-density lipoprotein, but not fucoidin or acetoacetylated low-density lipoprotein, markedly reduced the intensity of fluorescent cells. Preincubation in 10% fetal bovine serum resulted in fluorescent low-density lipoprotein labeling of only 75% of smooth muscle cells, which were also less fluorescent than those maintained in lipoprotein-deficient media. Fewer than 10% of smooth muscle cells exhibited any fluorescence with labeled acetoacetylated low-density lipoprotein.

Discussion

Our results show that corneal endothelium expresses receptors that mediate specific uptake of low-density lipoprotein. In contrast to vascular endothelium, which possesses large numbers of acetoacetylated low-density lipoprotein receptors, corneal endothelial cells internalize acetoacetylated low-density lipoprotein much less efficiently, which indicates limited, if any, scavenger receptor activity. The increases in low-density lipoprotein receptor activity that we observed in corneal endothelial cells after lipoprotein deprivation suggest that low-density lipoprotein receptors are regulated by cellular cholesterol stores through feedback mechanisms similar to those described for other cell types.[6,7]

Low-density lipoprotein binding has been reported in sparse and nonconfluent cultures of bovine corneal endothelial cells but not in confluent cultures.[23] Our results, however, demonstrate that intact human endothelial monolayers of whole corneas and confluent regions in human and monkey corneal endothelial cultures bind and internalize significant amounts of low-density lipoprotein. Nonconfluent areas of our primate corneal endothelial cell cultures, particularly cells at the growing margins, did show significantly more low-density lipoprotein incorporation than confluent regions in the same cultures composed of abutting, polygonal cells. Our results corroborate the reductions of low-density lipoprotein receptor activity observed in vascular endothelial cell and fibroblast cultures at high cell density or confluence.[24,25] These variations in low-density lipoprotein receptor expression appear to be regulated by the increased cholesterol requirements of proliferating cells and reduced requirements of confluent cells in which cell division is contact-inhibited.[26]

Moreover, in our model of endothelial injury on whole human corneas, we found cells surrounding areas of cell loss to increase their low-density lipoprotein uptake markedly. This observation is probably caused by increased

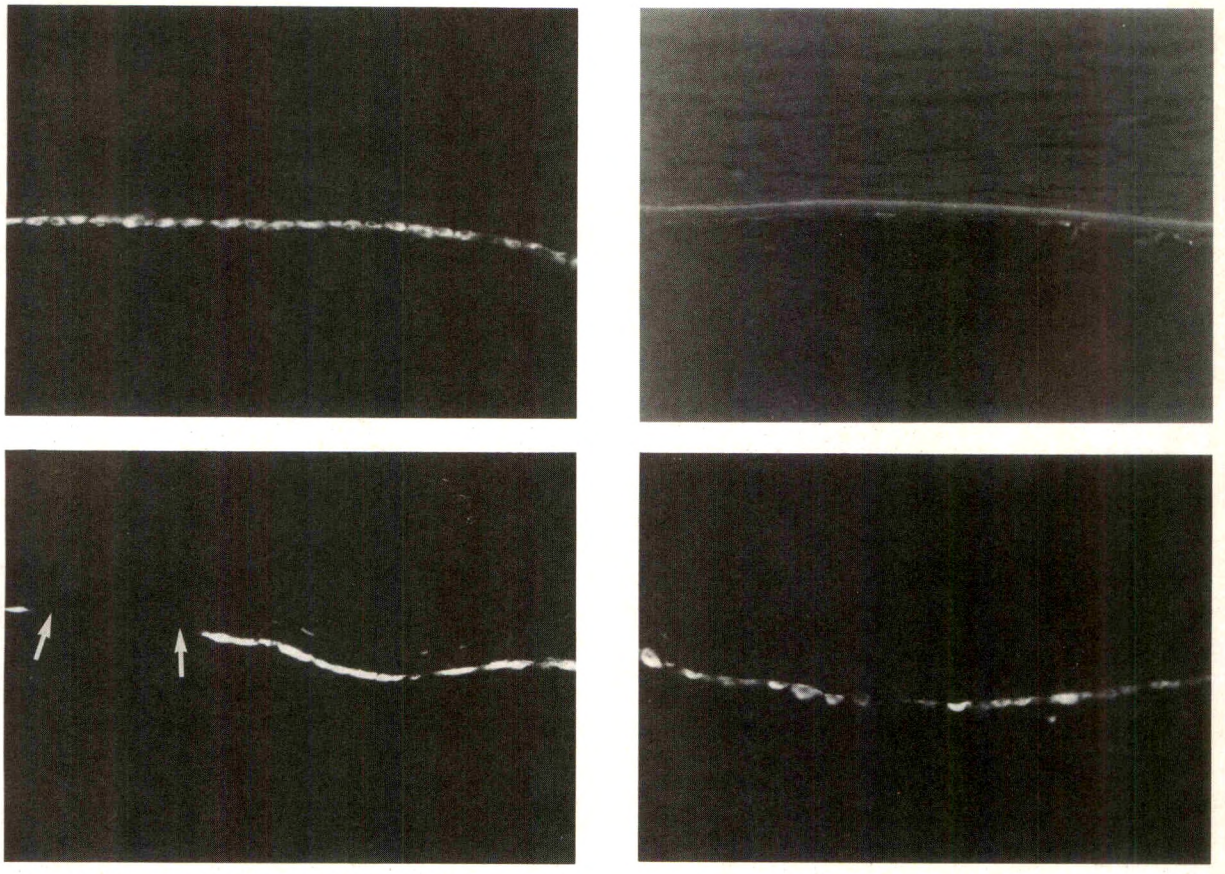


Fig. 3 (Elner and associates). Top left, Fluorescent low-density lipoprotein uptake by intact corneal endothelial cell monolayer of whole human cornea. Virtually all of the cells have internalized fluorescent low-density lipoprotein (15 μg/ml) (×200). Top right, Competition with unlabeled low-density lipoprotein effectively inhibited labeled low-density lipoprotein uptake. Minimal, if any, acetoacetylated low-density lipoprotein (15 μg/ml) uptake by corneal endothelium is seen in this overexposed photomicrograph (×200). Bottom left, Incubation with fluorescent low-density lipoprotein (15 μg/ml) 24 hours after scratch injury to the endothelial surface of whole human cornea. Intense fluorescence is seen in the spreading endothelial cells immediately adjacent to the area of cell loss (arrows), which is entirely nonfluorescent (×200). Bottom right, Cells distant from areas of injury in the same cornea exhibited levels of fluorescence similar to those seen in uninjured monolayers (×200).

numbers of low-density lipoprotein receptors present on growing or compromised cells.[6,7] In ocular diseases or injury causing breakdown of the blood-aqueous barrier, lipid and protein provided by low-density lipoprotein may be important to repair corneal endothelial membranes and supply components necessary for increased membrane production required by spreading cells reconstituting the endothelial monolayer.

Low-density lipoprotein receptor expression can also be influenced by growth-dependent and growth-independent effects of serum components, which may enter the eye with breakdown of the blood-aqueous barrier. For example, platelet-derived growth factor may directly enhance low-density lipoprotein receptor activity of quiescent cells[27,28] or amplify low-density lipoprotein receptor activity by causing increased cellular proliferation and proliferation-associated increases in low-density lipoprotein receptor production.[29] Low-density lipoprotein receptor activity is also modulated by heparin-binding growth factor–1 and various serum factors.[31,32] Although limited in their ability to proliferate after injury, human corneal endothelial cells may be induced to replicate by mesodermal growth factor[32] and other serum factors,[33] whose effects on corneal endothelial low-density lipoprotein receptor expression are

unknown. It is possible that these proliferation-enhancing factors may act in part by effects on low-density lipoprotein receptor activity. Alternatively, factors stimulating low-density lipoprotein receptor expression may promote the effects of agents enhancing corneal endothelial proliferation.[8] Low-density lipoprotein receptor activity is suppressed by prostaglandin E_1[34] and augmented by beta-adrenergic antagonists,[35] two agents of possible clinical importance with respect to ocular inflammation and drug therapy, respectively.

The leakage of circulating low-density lipoprotein caused by blood-aqueous barrier breakdown in a variety of ocular diseases and after surgical and nonsurgical trauma may provide a rich source of lipid and protein that may be efficiently incorporated by corneal endothelial cells for essential reparative functions. The rapid uptake of low-density lipoprotein may facilitate the repair of corneal endothelial membranes and the production of increased cell membrane required by cells spreading to regenerate an intact, functional monolayer damaged by inflammation, infection, or trauma. Our findings also illuminate basic mechanisms underlying the repair of human corneal endothelial cell membranes and metabolic requirements for endothelial proliferation. The identification of these specific receptor-mediated mechanisms in human corneal endothelium provides new information for the development of interventions aimed at enhancing corneal endothelial cell survival in ocular disease and after intraocular surgery.

ACKNOWLEDGMENT

The Michigan Eye Bank and Transplantation Center and the Illinois Eye Bank provided human eye tissue.

References

1. Capella, J. A.: Regeneration of endothelium in diseased and injured corneas. Am. J. Ophthalmol. 74:810, 1972.

2. Van Horn, D. L., and Hyndiuk, R. A.: Endothelial wound repair in primate cornea. Exp. Eye Res. 21:113, 1975.

3. Doughman, D. J., Van Horn, D., Rodman, W. P., Byrnes, P., and Lindstrom, R. L: Human corneal endothelial layer repair during organ culture. Arch. Ophthalmol. 94:1791, 1976.

4. Spencer, W. H.: Cornea. In Spencer, W. H. (ed.): Ophthalmic Pathology. An Atlas and Textbook, ed. 3, vol. 1. Philadelphia, W. B. Saunders, 1985, pp. 259–260.

5. Goldstein, J. L., and Brown, M. S.: The low-density lipoprotein pathway and its relation to atherosclerosis. Ann. Rev. Biochem. 46:897, 1977.

6. Brown, M. S., and Goldstein, J. L.: Regulation of the activity of the low density lipoprotein receptor in human fibroblasts. Cell 6:307, 1975.

7. Russell, D. W., Yamamoto, T., Schneider, W. J., Slaughter, C. J., Brown, M. S., and Goldstein, J. L.: cDNA cloning of the bovine low density lipoprotein receptor. Feedback regulation of a receptor mRNA. Proc. Natl. Acad. Sci. U.S.A. 80:7501, 1983.

8. Libby, P., Miao, P., Ordovas, J. M., and Schaefer, E. J.: Lipoproteins increase growth of mitogen-stimulated arterial smooth muscle cells. J. Cell. Physiol. 124:1, 1985.

9. Lange, Y., and Ramos, B. V.: Analysis of the distribution of cholesterol in the intact cell. J. Biol. Chem. 258:15130, 1983.

10. Mahley, R. W., Innerarity, T. L., Weisgraber, K. H., and Oh, S. Y.: Altered metabolism (in vivo and in vitro) of plasma lipoproteins by selective chemical modification of lysine residues of the apoproteins. J. Clin. Invest. 64:743, 1979.

11. Goldstein, J. L., Ho, Y. K., Basu, S. K., and Brown, M. S.: Binding on macrophages that mediates uptake and degradation of acetylated low-density lipoprotein, producing massive cholesterol deposition. Proc. Natl. Acad. Sci. U.S.A. 76:333, 1979.

12. Fogelman, A. M., Schechter, I., Seager, J., Hokom, M., Child, J. S., and Edwards, P. E.: Malondialdehyde alteration of low-density lipoprotein leads to cholesterol ester accumulation in human monocyte-macrophages. Proc. Natl. Acad. Sci. U.S.A. 77:2214, 1980.

13. Polacek, D., Byrne, R. E., and Scanu, A. M.: Modification of low density lipoproteins by polymorphonuclear cell elastase leads to enhanced lipoprotein receptor pathway. J. Lipid Res. 29:797, 1988.

14. Steinbrecher, U. P., Parthasarathy, S., Leake, D. S., Witztum, J. L., and Steinberg, D.: Modulation of low density lipoprotein by endothelial cells involves lipid peroxidation and degradation of low density lipoprotein phospholipids. Proc. Natl. Acad. Sci. U.S.A. 81:3883, 1984.

15. Stein, O., and Stein, Y.: Bovine aortic endothelial cells display macrophage-like properties towards acetylated ^{125}I-labelled low density lipoprotein. Biochim. Biophys. Acta 620:631, 1980.

16. Haberland, M. E., Rasmussen, R. R., Olch, C. L., and Fogelman, A. M.: Two distinct receptors account for recognition of maleyl-albumin in human monocytes during differentiation in vitro. J. Clin. Invest. 77:681, 1986.

17. Sparrow, C. P., Parthasarathy, S., and Steinberg, D.: A macrophage receptor that recognizes oxidized low density lipoprotein but not acetylated low density lipoprotein. J. Biol. Chem. 264:2599, 1989.

18. Yue, B. Y. J. T., Sugar, J., Gilboy, J. E., and Elvart, J. L.: Growth of human corneal endothelial

cells in culture. Invest. Ophthalmol. Vis. Sci. 30:248, 1989.

19. Yue, B. Y. J. T., and Baum, J. L.: Studies of corneas in vivo and in vitro. Vision Res. 21:41, 1981.

20. Hass, A. J., Davis, H. R., Elner, V. M., and Glagov, S.: Identification of macrophages in sections of rabbit lungs using acetoacetylated lipoproteins. J. Histochem. Cytochem. 31:1136, 1983.

21. Pitas, R. E., Innerarity, T. L., Weinstein, J. N., and Mahley, R. W.: Acetoacetylated lipoproteins used to distinguish fibroblasts from macrophages in vitro by fluorescence microscopy. Arteriosclerosis 1:177, 1981.

22. Brown, M. S., Basu, S. K., Flack, J. R., Ho, Y. K., and Goldstein, J. L.: The scavenger cell pathway for lipoprotein degradation. Specificity of the binding site that mediates the uptake of negatively-charged LDL by macrophages. J. Supramol. Struct. 13:67, 1980.

23. Gospodarowicz, D., Vlodavsky, I., Greenburg, G., Alvarado, J., Johnson, L. K., and Moran, J.: Studies on atherogenesis and corneal transplantation using cultured vascular and corneal endothelia. Recent Prog. Horm. Res. 35:375, 1979.

24. Vlodavsky, I., Fielding, P. E., Fielding, C. J., and Gospodarowicz, D.: Role of contact inhibition in the regulation of receptor-mediated uptake of low density lipoprotein in cultured vascular endothelial cells. Proc. Natl. Acad. Sci. U.S.A. 75:356, 1979.

25. Kruth, H. S., Avignan, J., Gamble, W., and Vaughn, M.: Effect of cell density on binding and uptake of low density lipoprotein by human fibroblasts. J. Cell Biol. 83:588, 1979.

26. Kenagy, R., Bierman, E. L., and Schwartz, S.: Regulation of low density lipoprotein metabolism by cell density and proliferative state. J. Cell. Physiol. 116:404, 1983.

27. Chait, A., Ross, R., Albers, J. J., and Bierman, E. L.: Platelet-derived growth factor stimulates activity of low-density lipoprotein receptors. Proc. Natl. Acad. Sci. U.S.A. 77:4084, 1980.

28. Witte, L. D., Cornicelli, J. A., Miller, R. W., and Goodman, D. S.: Effects of platelet-derived and endothelial cell-derived growth factors on the low density lipoprotein receptor pathway in cultured human fibroblasts. J. Biol. Chem. 257:5392, 1982.

29. Mazzone, T., Basheeruddin, K., Ping, L., Frazer, S., and Getz, G. S.: Mechanism of the growth-related activation of the low density lipoprotein receptor pathway. J. Biol. Chem. 264:1787, 1989.

30. Ellsworth, J. L., Brown, C., and Cooper, A. D.: Stimulation of LDL receptor activity in Hep-G2 cells by a serum factor(s). J. Cell. Physiol. 135:213, 1988.

31. Chen, J. K., Hoshi, H., and McKeehan, W. L.: Heparin-binding growth factor type one and platelet-derived growth factor are required for the optimal expression of cell surface low density lipoprotein receptor binding activity in human adult arterial smooth muscle cells. In Vitro 24:199, 1987.

32. Squires, E. L., and Weimar, V. L.: Stimulation of repair of human corneal endothelium in organ culture by mesodermal growth factor. Arch. Ophthalmol. 98:1462, 1980.

33. Schultz, G. S., Woost, P. G., and Eiferman, R. A.: Modification of corneal wound healing by growth factors. In Cavanagh, H. D. (ed.): The Cornea. Transactions of the World Congress on the Cornea III. New York, Raven Press, 1988, pp. 15–21.

34. Krone, W., Klass, A., Nagele, H., Behnke, B., and Greten, H.: Prostaglandin E1 suppresses low density lipoprotein receptor activity and cholesterol synthesis in human mononuclear leukocytes. Prog. Clin. Biol. Res. 242:337, 1987.

35. Bernini, F., Corsini, A., Allorio, M., Musanti, R., and Fumagalli, R.: Lipophilic beta-adrenoceptor antagonists stimulate low density lipoprotein receptor activity in human skin fibroblasts. Pharmacology 34:225, 1987.

OPHTHALMIC MINIATURE

Chee stopped, eyes on Pinto. The man sat as still as death, waiting. His skin was drawn tight over the skull bones, seeming almost transparent in its thinness. The desiccation made his eyes seem protuberant, larger than they were. They were black eyes, but the cornea of one was clouded by a film of cataract.

Tony Hillerman, *Coyote Waits*
New York, Harper & Row, Publishers, 1990, p. 133

Epidemiologic Characteristics, Predisposing Factors, and Etiologic Diagnosis of Corneal Ulceration in Nepal

Madan P. Upadhyay, M.D., Purna C. D. Karmacharya, M.D., Shasank Koirala, M.D., Nhuchhe R. Tuladhar, B.S., Larry E. Bryan, M.D., Gilbert Smolin, M.D., and John P. Whitcher, M.D.

Corneal ulceration is one of the most frequent causes of blindness in developing countries. Between September 1985 and August 1987, 405 patients with corneal ulceration were examined at Tribhuvan University Teaching Hospital in Kathmandu, Nepal. Males and females were equally affected. The most common predisposing cause of ulceration was corneal trauma, usually with organic agricultural materials. Microorganisms were grown from 324 (80%) of the ulcers. Pure bacterial cultures were obtained from 256 (63.2%) of the patients, whereas pure fungal cultures were obtained from 27 (6.7%) of the patients. In 41 patients (10.1%), corneal cultures yielded a mixed growth of bacteria and fungi. Of a total of 398 bacterial isolates, 124 (31.1%) were positive for *Streptococcus pneumoniae*, the most commonly isolated organism in the series. Other frequently isolated bacteria included *Staphylococcus epidermidis*, *S. aureus*, and *Pseudomonas* species. Of 68 positive fungal isolates obtained, 32 (47.0%) were identified as *Aspergillus* species. *Candida* species and *Fusarium* species were less commonly seen.

Accepted for publication Oct. 12, 1990.

From the Department of Ophthalmology, Tribhuvan University, Institute of Medicine, Kathmandu, Nepal (Drs. Upadhyay, Karmacharya, and Koirala, and Mr. Tuladhar); Department of Microbiology, University of Calgary, Calgary, Canada (Dr. Bryan); and Francis I. Proctor Foundation for Research in Ophthalmology, University of California San Francisco, San Francisco, California (Drs. Smolin and Whitcher). This study was supported by a grant from the International Development Research Center, Ottawa, Canada, in collaboration with the Department of Microbiology, University of Calgary, Calgary, Canada, and by assistance from the Francis I. Proctor Foundation and the Albert and Lotte Haas Foundation, San Francisco, California.

Reprint requests to Madan P. Upadhyay, M.D., Tribhuvan University, Institute of Medicine, Box 2162, Kathmandu, Nepal; or John P. Whitcher, M.D., Francis I. Proctor Foundation, 95 Kirkham St., San Francisco, CA 94143-0944.

In the developing countries of the world, corneal ulceration is a major cause of blindness. This situation is especially true in areas where trachoma, onchocerciasis, leprosy, and other infectious causes of ocular disease are endemic. As a result, corneal opacification is second only to cataract as the most important cause of visual disability in the world today.[1] Studies from several developing countries have reported the incidence of bacterial and fungal pathogens isolated from ulcerated corneas.[2-6] Comprehensive epidemiologic surveys investigating the predisposing and demographic factors contributing to corneal ulceration, however, are rare.[7,8] Since the epidemiologic pattern of corneal ulceration varies significantly from region to region, an understanding of the epidemiologic pattern in different parts of the world is essential for the development of a global strategy for prevention of blindness caused by corneal ulceration.

Nepal is a landlocked country occupying the southern slopes of the Himalayas. The nationwide blindness prevalence rate is 0.84%. With a population of approximately 18 million, Nepal has the same number (100,857) of noninstitutionalized blind people as the United States (101,000).[9] Cataract is the most common cause of visual loss in Nepal, accounting for more than 80% of all avoidable blindness. Corneal trauma and ulceration are the second leading cause of unilateral blindness in Nepal after cataract and are responsible for 7.9% of all blind eyes.[9] We attempted to evaluate the epidemiologic factors contributing to corneal ulceration in Nepal and to identify the specific bacterial and fungal pathogens responsible for microbial keratitis.

Patients and Methods

Patients with central corneal ulcers were all examined at the Department of Ophthalmology, Tribhuvan University Teaching Hospital in Kathmandu, Nepal. Between September 1985 and August 1987, we examined 405 patients with microbial keratitis. Typical viral ulcers and healing corneal ulcers were excluded. Sociodemographic information and personal data on all patients with corneal ulceration were collected on a standardized form. The date of onset of the illness, the time elapsed before seeking medical attention, a brief narrative history of the illness, predisposing ocular conditions, previous treatment, and associated risk factors, such as malnutrition, poor hygiene, or concurrent systemic diseases, were documented.

Each patient was examined with the biomicroscope by an ophthalmologist, and a clinical diagnosis was made. Corneal ulceration was defined as loss of the corneal epithelium with clinical evidence of infection with or without hypopyon. Associated clinical findings, such as blepharitis, conjunctivitis, trichiasis, and corneal exposure, were noted. The patients were also examined for other diseases, such as leprosy or trachoma, which would predispose them to corneal ulceration.

After detailed examination of the affected eye, the corneal ulcer was scraped under aseptic conditions with a flame-sterilized Kimura spatula. Scrapings were performed by the ophthalmologist with the biomicroscope without instillation of an anesthetic preparation.[10] Twenty-nine children required ketamine hydrochloride as a general anesthetic for corneal scraping.

Material from scrapings was inoculated directly onto blood, chocolate, and Sabouraud dextrose agars, and into brain heart infusion broth both with and without 50 mg/ml of gentamicin sulfate. Cultures were collected and incubated aerobically according to standard protocols.[11] Material was also inoculated on blood agar and incubated anaerobically in the Baltimore Biological Laboratory gas-pack system. A portion of the material collected with the Kimura platinum spatula was smeared on four glass slides and stained with Gram stain, Giemsa stain, and Gomori methenamine-silver stain. The fourth slide was held in reserve. In 305 cases, samples were also inoculated onto nonnutrient agar overlaid with *Escherichia coli* in an attempt to isolate *Acanthamoeba* species.

Aerobic bacterial cultures were examined at 24 hours and daily thereafter. Cultures were recorded as negative if there was no growth after 96 hours. Anaerobic bacterial cultures in the Baltimore Biological Laboratory anaerobic gas-pack system were examined after 48 hours. In the last consecutive 305 cases, samples were also inoculated into Ogawa medium (Eiken Co., Japan) for mycobacteria and were incubated for up to eight weeks. Fungal cultures were incubated in Sabouraud dextrose agar at 27 C for four weeks and were examined daily for a week and on alternate days for the remaining three weeks. Brain heart infusion broth cultures with gentamicin sulfate were incubated in a shaking water bath at 110 oscillations per minute at 27 C and examined daily for three days. Brain heart infusion broth showing no growth after three days was considered negative. Samples inoculated in nonnutrient agar overlaid with *E. coli* were examined daily for four days for signs of *Acanthamoeba* species.

A culture from a patient was considered positive if one of the three following conditions was met: the same organism was present on more than one culture medium; there was semiconfluent growth at the site of the inoculation on one solid medium; or there was heavy growth within a single liquid medium confirmed by a positive-stained corneal smear.

Bacteria were identified on the basis of their morphologic characteristics, staining characteristics, and biochemical properties. Filamentous fungi were identified by their colony characteristics and microscopic appearance in lactophenol cotton blue preparation. Nonfilamentous fungi were identified by their colony characteristics, microscopic appearance, germ tube test, and biochemical properties.

Results

Of the 405 patients, 208 were males and 197 were females. Ulceration occurred most frequently in patients 41 to 50 years of age and was rare in the extremely young or the extremely old (Figure). In general, ulceration was evenly distributed between males and females in all age groups, except in the 11- to 20-year-olds and in the 61- to 70-year-olds, in whom twice as many males as females had ulcers.

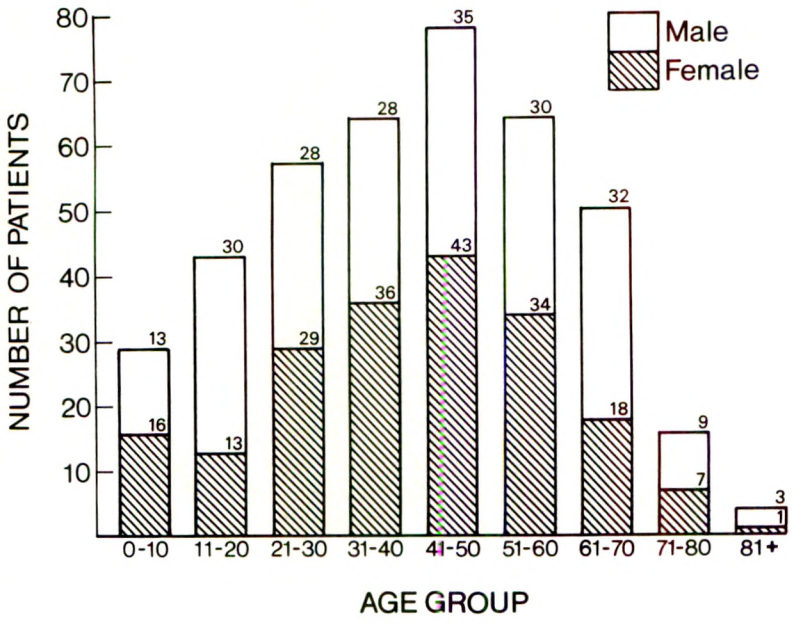


Figure (Upadhyay and associates). Age and sex distribution of patients with corneal ulceration in Nepal.

Of the 405 patients, 201 (49.6%) were employed as farmers at the time of the study. The remaining patients' occupations reflect the economic pattern of employment in the Kathmandu Valley and surrounding areas. Homemakers were next most frequently seen (91 patients, 22.5%), followed by students (40 patients, 9.9%), office workers (28 patients, 6.9%), children 6 years of age and younger (20 patients, 4.9%), and laborers (14 patients, 3.5%).

Patients were also questioned about the duration of their symptoms. A total of 177 (43.7%) patients were examined within the first seven days after the onset of the illness (Table 1). Of these patients who were examined early, 110 (80.5%) were from within Kathmandu Valley. Most of the patients with corneal ulceration, 228 (56.3%), came for examination later than one week after onset of their symptoms, and 73 patients (18.1%) were not examined until a month or more had elapsed from the onset of their first ocular symptoms.

Many of the patients had sought medical and nonmedical help before initial examination at the Ophthalmology Clinic, Tribhuvan University Teaching Hospital. Of 405 patients, 273 (67.4%) had some form of consultation before examination and corneal scrapings were performed. A total of 192 patients (47.4%) had previously been examined and partially treated by health care workers, paramedics, physicians, or ophthalmologists. Another 81 patients (20.0%) were treated by traditional healers. The remaining 132 patients (32.6%) had not received any treatment before examination at the Ophthalmology Clinic.

Factors predisposing to corneal ulceration were reported in 346 of 405 patients (85.4%). The most common local factor reported was trauma to the cornea in 214 patients (52.8%). The agents responsible for trauma were mainly organic materials to which farmers are exposed, including rice paddy stalks, dust, grass, wood, and animal products. None of the patients wore contact lenses.

Other predisposing conditions included eye-

TABLE 1
DURATION OF ILLNESS BEFORE EVALUATION AT TRIBHUVAN UNIVERSITY TEACHING HOSPITAL EYE CLINIC

DURATION OF ILLNESS	OUTSIDE OF KATHMANDU VALLEY (N = 214)	WITHIN KATHMANDU VALLEY (N = 185)	UNKNOWN (N = 6)	TOTAL (%) (N = 405)
1–7 days	64	110	3	177 (43.7)
8–14 days	45	34	2	81 (20.0)
15–29 days	47	22	—	69 (17.0)
1–2 months	28	15	—	43 (10.6)
2–3 months	13	1	—	14 (3.5)
> 3 months	14	2	—	16 (4.0)
Unspecified	3	1	1	5 (1.2)

TABLE 2
MICROBIAL GROWTH PATTERN IN 405 CONSECUTIVE CORNEAL ULCERS

GROWTH PATTERN	NO. OF CASES	PERCENTAGE
Pure bacterial growth		
Single species of bacteria	182	44.9
Multiple species of bacteria*	74	18.3
Pure fungal growth		
Single species of fungi	27	6.7
Mixed microbial growth†		
Single species of bacteria with fungi	30	7.4
Multiple species of bacteria with fungi	11	2.7
Cases with positive cultures	324	80.0
Cases with negative cultures	81	20.0

*161 bacterial species isolated.
†55 bacterial species isolated.

lid diseases such as blepharitis, trichiasis, entropion, or ectropion in 24 patients (6.0%), dacryocystitis in nine patients (2.2%), acute conjunctivitis in 58 patients (14.3%), and a variety of systemic diseases including xerophthalmia, tuberculosis, diabetes, measles, malnutrition, and poor general hygiene in 41 patients (10.1%). These risk factors exclusive of corneal trauma were responsible for ulceration in 132 patients (32.6%).

Microorganisms were grown from 324 (80.0%) of the 405 corneal ulcers (Table 2). Of the 405 cultures, 256 (63.2%) exhibited pure bacterial growth, although 74 of the cultures grew multiple species of bacteria (a total of 161 bacterial species were isolated). Pure fungal growth was present in 27 (6.7%) of all cases of corneal ulceration, and 41 cultures (10.1%) yielded a mixed growth of both bacteria and fungi (a total of 55 bacterial species were isolated). Fungi were grown from a total of 68 corneal ulcers, of which two thirds also had positive bacterial cultures. Infections with multiple species of fungi were not encountered.

Microbial growth was present in 172 of 223 cases (77.1%) despite previous treatment with antibiotics, and in 38 of 43 patients (88.4%) who had been previously treated with herbal medicine (Table 3). Only 14 patients (3.4%) were found to have been treated with corticosteroids alone or in combination with antibiotics before examination. Of these patients, 11 cultures (78.6%) showed microbial growth. Of the 125 patients (30.9%) who received no treatment, 103 cultures (82.4%) showed microbial growth.

Bacterial organisms isolated from corneal ulcers consisted of 28 species from 18 genera (Table 4). Of the total of 398 bacterial isolates, 299 (75.1%) were gram-positive and 99 (24.9%) were gram-negative. *Streptococcus pneumoniae* was the most commonly isolated bacterial organism in the series, accounting for 124 (31.1%) of all positive bacterial cultures. The next most common gram-positive organisms seen were *Staphylococcus epidermidis* (11.5%) and *Staphylococcus aureus* (10.8%). *Streptococcus viridans* also occurred frequently (5.2%) as well as *Corynebacterium xerosis* (11.9%).

Pseudomonas species was the most frequently isolated gram-negative bacterium, accounting for 42 positive cultures (10.6%). This was followed by *Acinetobacter calcoaceticus* (4.0%), *Moraxella* species (2.0%), and *Haemophilus influenzae* (1.8%).

Propionibacterium acnes was the only anaerobic bacterial organism isolated from the cornea, accounting for three cases. *Acanthamoeba* spe-

TABLE 3
CORRELATION OF MICROBIAL GROWTH WITH PREVIOUS TREATMENT

TREATMENT*	BACTERIA ISOLATED (N = 256)	FUNGI ISOLATED (N = 27)	MIXED ISOLATED (N = 41)	NONE ISOLATED (N = 81)	TOTAL CASES (N = 405)	(%)
Antibiotics alone	128	20	24	51	223	(55.1)
Corticosteroids alone	1	0	2	0	3	(0.7)
Antibiotics and corticosteroids	3	2	3	3	11	(2.7)
Herbal medicine alone	34	1	3	5	43	(10.6)
No treatment	90	4	9	22	125	(30.9)

*Patients were usually treated with topical antibiotics commonly available from local pharmacies. These included sodium sulfacetamide, chloromycetin, tetracycline, and gentamicin.

TABLE 4
BACTERIAL ISOLATES FROM CORNEAL ULCERS IN NEPAL

BACTERIA	SINGLE SPECIES ISOLATED	MIXED WITH OTHER BACTERIA	MIXED WITH FUNGI	TOTAL (%)
	Gram-Positive Organisms Isolated			
Streptococcus pneumoniae	85	31	8	124 (31 1)
Staphylococcus epidermidis	18	20	8	46 (11.5)
S. aureus	16	19	8	43 (10.8)
St. viridans	3	14	4	21 (5.2)
Micrococcus tetragens	3	5	2	10 (2.5)
St. pyogenes	1	—	1	2 (0.5)
St. faecalis	1	—	—	1 (0.3)
Propionibacterium acnes	—	1	2	3 (0.7)
Listeria monocytogenes	1	—	—	1 (0.3)
Nocardia asteroides	1	—	—	1 (0.3)
Corynebacterium xerosis	11	27	9	47 (11.9)
	Gram-Negative Organisms Isolated			
Pseudomonas species*	22	14	6	42 (10.6)
Acinetobacter calcoaceticus	7	8	1	16 (4.0)
Moraxella species†	1	7	—	8 (2.0)
Haemophilus influenzae	2	3	2	7 (1.8)
Citrobacter freundii	3	3	1	7 (1.8)
Enterobacter aerogenes	3	2	1	6 (1.5)
Branhamella catarrhalis	1	3	1	5 (1.2)
Escherichia coli	1	1	1	3 (0.7)
Klebsiella species‡	1	1	—	2 (0.5)
Proteus mirabilis	—	2	—	2 (0.5)
Serratia marcescens	1	—	—	1 (0.3)
Total (Percentage)	182 (45.7)	161 (40.5)	55 (13.8)	398 (100.0)

**Pseudomonas* species isolated include *P. aeruginosa* (41) and *P. fluorescens* (1).
†*Moraxella* species isolated include *M. liquefaciens* (3) and *M. nonliquefaciens* (5).
‡*Klebsiella* species isolated include *K. pneumoniae* (1) and *K. rhinoscleromatis* (1).

cies was not isolated in any case, and cultures for *Mycobacterium* species performed on the last consecutive 305 patients in the series were negative.

Although the number of fungal corneal ulcers was much smaller than the number of bacterial ulcers, 68 positive fungal cultures were obtained. Fungal elements were demonstrated on direct corneal smears from 38 of the patients (55.4%) with positive fungal cultures. In 32 of these 38 cases, fungal elements were seen by both Gram stain and Gomori methenamine-silver, and in six cases fungi were seen with Gomori methenamine-silver only.

A total of 36 species of fungal organisms from 15 genera were identified (Table 5). Of 68 total isolates, 31 were of *Aspergillus* species (47.0%), followed by nine of *Candida* species (13.2%), and eight of *Fusarium* species (11.7%). In most of the cases, the fungal organisms that were isolated were mixed with bacteria (Table 2). All of the fungi grew within 15 days either in Sabouraud dextrose agar, brain heart infusion broth, or both. Only six of the 68 positive cultures were grown in brain heart infusion broth only.

Discussion

In Nepal, corneal trauma and ulceration are the second leading cause of unilateral blind-

TABLE 5
FUNGAL ISOLATES FROM CORNEAL ULCERS IN NEPAL

FUNGI	PURE ISOLATES	MIXED WITH BACTERIA	TOTAL (%)
Aspergillus species*	14	18	31 (47.0)
Candida species†	2	7	9 (13.2)
Fusarium species‡	4	4	8 (11.7)
Cladosporium species§	—	4	4 (5.9)
Mucor species‖	—	3	3 (4.4)
Lasiodiplodia theobromae	1	2	3 (4.4)
Curvularia prasadii	1	1	2 (2.9)
Collectotrichum capsici	1	—	1 (1.5)
Nigrospora sphaerica	—	1	1 (1.5)
Phialophora cycliminis	1	—	1 (1.5)
Penicillium griseofulvum	—	1	1 (1.5)
Rhizopus pusillus	1	—	1 (1.5)
R. arrhizus	1	—	1 (1.5)
Sporotrichum carnis	1	—	1 (1.5)
Total (Percentage)	27 (39.7)	41 (60.3)	68 (100.0)

*_Aspergillus_ species isolated include _A. fumigatus_ (18), _A. flavus_ (8), _A. restricuts_ (1), _A. ustus_ (1), _A. versicolor_ (1), _A. sydowii_ (1), _A. terreus_ (1), and _A. oryzae_ (1).

†_Candida_ species isolated include _C. krusei_ (2), _C. tropicalis_ (2), _C. pseudotropicalis_ (1), _C. parapsilosis_ (1), _C. guilliermondii_ (2), and _Geotrichum candidum_ (1).

‡_Fusarium_ species isolated include _F. oxysporum_ (2), _F. solani_ (1), _F. heterospermum_ (2), _F. nivale_ (1), _F. sporotrichoides_ (1), and _F. tabacinum_ (1).

§_Cladosporium_ species isolated include _C. chlorocephalum_ (2), _C. cladosporoides_ (1), and _C. sphaerospermum_ (1).

‖_Mucor_ species isolated include _M. globosus_ (1), _M. mucedo_ (1), and _M. racemosus_ (1).

ness.[9] In contrast to the visual loss from cataracts, which affects mainly the older age groups, corneal ulceration is encountered in all ages. This pattern is similar to that reported from populations studied in other countries.[12-16] Even though trauma was rarely reported as a predisposing cause of corneal ulceration in children in Nepal, probably because of their lack of participation in agricultural activity, other factors, such as malnutrition, xerophthalmia, and measles, were frequently seen and were directly responsible for one third of all cases of microbial keratitis in the newborn to 11-year-old age group.

The occupations of the patients in the study reflect the economic patterns of employment in Kathmandu Valley and the surrounding countryside. Since 95% of Nepalese (both males and females) are engaged in agricultural activity with rice as the main crop, corneal injury from a rice stalk, not surprisingly, represents the single greatest risk factor found in the study. Absent in this group of patients were contact lens wearers and individuals with compromised corneas caused by disease processes, such as herpes simplex keratitis, keratoconjunctivitis sicca, or bullous keratopathy, which are frequently implicated as causes of corneal ulceration in the developed countries of the world.[17-19]

In this study, 177 of the 405 patients (43.7%) came to the Ophthalmology Clinic for consultation after they had ocular symptoms for more than a week, and 73 (18.1%) of the patients came to the clinic one month or more after the onset of their symptoms. As a consequence, most of the ulcers were advanced at the time of first examination. Two thirds of the patients had sought help from either health care workers, physicians, or traditional healers before examination, but one third of all the patients had no previous treatment.

Microorganisms were isolated from 80% of the 405 corneas that were cultured. This high rate of recovery of organisms compares favorably with other studies,[5,14,20,21] and was primarily because of multiple scrapings from the area of ulceration and to a lesser extent to the use of several enriched culture media for inoculation. Despite the use of topical antibiotics by 223 of the patients before examination, organisms were cultured in 172 of the 223 patients (77.1%), which indicates the use of inappropriate antibiotics or poor patient compliance. Only 14 of the 405 patients were previously treated with topical corticosteroids or with antibiotics in combination with corticosteroids. Of these, 11 of the 14 had positive cultures for fungal organisms. Even though the number of patients previously treated with corticosteroids was small, it appears that the recovery of fungal organisms from those patients was definitely enhanced by corticosteroid therapy.

Even though the most commonly isolated bacteria in this series were *Streptococcus pneumoniae* (31.1%) and *Staphylococcus* species (22.3%), *Corynebacterium xerosis* or diphtheroids were also isolated in large numbers (11.9%). Although these latter organisms have been considered nonpathogenic for the cornea, their presence in chronic corneal ulcers that are otherwise sterile has led to speculation that they may be indolent pathogens.[22]

In the United States, the incidence of *Streptococcus pneumoniae* as a corneal pathogen has fallen to less than 7%,[23,24] whereas *Pseudomonas* species has become the most frequently isolated pathogen in several series.[17-20,23] This increase in the frequency of pseudomonad corneal ulceration has led to the false assumption that *Pseudomonas* species is the most common cause of ulceration in the world. Studies in developing countries of the epidemiology of corneal ulceration, however, demonstrate a much more variable etiologic pattern. *Streptococcus pneumoniae* has been reported as the most frequently isolated bacterial pathogen in patients with corneal ulceration by Pahalkar and associates[5] in south India as well as by Carmichael, Wolpert, and Koornhof[6] in South Africa. It is clearly evident that epidemiologic surveys are needed in each area to determine the bacterial pathogen most commonly responsible for ulceration. The problem is of grave practical concern because of the difference in therapeutic approach when treating a pneumococcal as opposed to a pseudomonad ulcer. Since *Streptococcus* species in general are not sensitive to aminoglycosides, use of gentamicin or tobramycin as first-line antibiotics for treating corneal ulcers in an area where *Streptococcus pneumoniae* is the primary pathogen is inappropriate.

The incidence of 16.8% fungal infection also demonstrates the severity of the problem of fungal corneal ulceration from an epidemiologic point of view. In Nepal, an enormous spectrum of pathogens was encountered in the corneas of infected patients, but *Aspergillus* species was isolated in almost half the cases. This finding is similar to previous reports.[25]

The emphasis of this study has been to develop a comprehensive epidemiologic cross section of central corneal ulceration in Nepal. Although a specific etiologic diagnosis was of paramount importance in the study, an attempt was also made to identify those demographic and personal factors that predispose an individual to the development of corneal ulceration. We believe that large-scale comprehensive epidemiologic surveys of this type are of great importance in delineating the pattern of disease and in identifying the specific pathogens responsible for infection. The importance of this type of survey has even greater meaning in the context of the limited health care resources available for the diagnosis and treatment of diseases that cause blindness in many of the developing nations of the world.

References

1. W.H.O. Weekly Epidemiol. Rec. 64:216, 1989.
2. Upadhyay, M. P., Rai, N. C., Brandt, F., and Shrestha, R. B.: Corneal ulcers in Nepal. Graefes Arch. Clin. Exp. Ophthalmol. 219:55, 1982.
3. Katz, N. N. K., Wadud, S. A., and Ayazuddin, M.: Corneal ulcer disease in Bangladesh. Ann. Ophthalmol. 15:834, 1983.
4. Mahajan, V. N.: Ulcerative keratitis. An analysis of laboratory data in 674 cases. J. Ocul. Ther. Surg. 4:138, 1985.
5. Pahalkar, S., Thomas, A., Alexander, T. A., and Koshi, G.: Bacterial and mycotic agents of corneal ulcers in Vellore. Indian J. Ophthalmol. 3:289, 1985.
6. Carmichael, T. R., Wolpert, M., and Koornhof, H. J.: Corneal ulceration in an urban African hospital. Br. J. Ophthalmol. 69:920, 1985.
7. Ormerod, L. D.: Causation and management of microbial keratitis in subtropical Africa. Ophthalmology 94:1662, 1987.
8. Di Bisceglie, A. M., and Carmichael, T. R.: Factors predisposing to central corneal ulceration in a developing population. S. Afr. Med. J. 71:769, 1987.
9. Brilliant, L. B., Pokhrel, R. P., Grasset, N. C., Lepkowksi, J., Kolstad, A., Hawks, W., Pararajasegaram, R., Brilliant, G. E., Gilbert, S., Shrestha, S. R., and Kuo, J.: Epidemiology of blindness in Nepal. Bull. W.H.O. 63:375, 1985.
10. Klienfield, J., and Ellis, P. P.: Inhibition of microorganisms by topical anesthetics. Appl. Microbiol. 15:1296, 1967.
11. Jones, D. B.: Early diagnosis and therapy of bacterial corneal ulcers. Int. Ophthalmol. Clin. 13:1, 1973.
12. Sharma, S. L.: Keratomycosis in corneal sepsis. Indian J. Ophthalmol. 29:443, 1981.
13. Dutta, L. C., Dutta, D., and Mahanty, P.: Study on fungal keratitis. Indian J. Ophthalmol. 29:407, 1981.
14. Ormerod, L. D., Linn Murphree, A., Gomez, D. S., Schanzlin, D. J., and Smith, R. E.: Microbial keratitis in children. Ophthalmology 93:449, 1986.
15. Foster, A., and Sommer, A.: Childhood blindness from corneal ulceration in Africa. Causes, prevention, and treatment. Bull. W.H.O. 64:619, 1986.
16. ———: Corneal ulceration, measles and childhood blindness in Tanzania. Br. J. Ophthalmol. 71:331, 1987.
17. Ormerod, L. D., and Smith, R. E.: Contact lens-associated microbial keratitis. Arch. Ophthalmol. 104:79, 1986.
18. Koidou-Tsiligianni, A., Alfonso, E., and Forster, R. K.: Ulcerative keratitis associated with contact lens wear. Am. J. Ophthalmol. 108:64, 1989.
19. Musch, D. C., Sugar, A., and Meyer, R. F.: Demographic and predisposing factors in corneal ulceration. Arch. Ophthalmol. 101:1545, 1983.
20. Liesegang, T. J., and Forster, R. K.: Spectrum

of microbial keratitis in south Florida. Am. J. Ophthalmol. 90:38, 1980.

21. Jones, D. B.: Initial therapy of suspected microbial corneal ulcer. II. Specific antibiotic therapy based on corneal smears. Surv. Ophthalmol. 24:97, 1979.

22. Rubinfeld, R. S., Cohen, E. J., Arentsen, J. J., and Laibson, P. R.: Diphtheroids as ocular pathogens. Am. J. Ophthalmol. 108:251, 1989.

23. Donnenfield, E. D., Cohen, E. J., and Arentsen, J. J.: Changing trends in contact lens-associated corneal ulcers. An overview of 116 cases. CLAO J. 12:145, 1986.

24. Ostler, B., Okumoto, M., and Wilkey, C.: The changing pattern of the etiology of central bacterial corneal (hypopyon) ulcer. Trans. Pac. Coast Otoophthalmol. Soc. 57:235, 1976.

25. Jones, B. R.: Principles in the management of oculomycosis. XXXI Edward Jackson Memorial Lecture. Am. J. Ophthalmol. 79:719, 1975.

OPHTHALMIC MINIATURE

"Tell me," I said, "you that so strain your breasts together, who are you?"

And they bent back their necks; and when they had raised their faces to me their eyes, which before were moist only within, gushed over at the lids, and the frost bound the tears between and locked them up again, never did clamp bind beam on beam so hard; whereupon they butted together like two goats, such fury mastered them.

The Divine Comedy of Dante Alighieri
Translated by John D. Sinclair, Canto XXXII of Inferno

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

EDITORIAL BOARD

Thomas M. Aaberg, *Atlanta*
Jules Baum, *Boston*
William M. Bourne, *Rochester*
Ronald M. Burde, *New York*
Fred Ederer, *Bethesda*
Frederick T. Fraunfelder, *Portland*
Michael A. Kass, *St. Louis*
Steven G. Kramer, *San Francisco*
Irving H. Leopold, *Irvine*
Robert Machemer, *Durham*
Nancy M. Newman, *San Francisco*
Don H. Nicholson, *Miami*
Edward W. D. Norton, *Miami*
Deborah Pavan-Langston, *Boston*
Allen M. Putterman, *Chicago*
Dennis Robertson, *Rochester*
Merlyn M. Rodrigues, *Baltimore*
Stephen J. Ryan, *Los Angeles*
Jerry A. Shields, *Philadelphia*
M. Bruce Shields, *Durham*
Ronald E. Smith, *Los Angeles*
Bruce E. Spivey, *San Francisco*
Bradley R. Straatsma, *Los Angeles*
H. Stanley Thompson, *Iowa City*
E. Michael Van Buskirk, *Portland*
Gunter K. von Noorden, *Houston*

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

Edward W. D. Norton, *President*
Bradley R. Straatsma, *Vice President*
Frank W. Newell, *Secretary and Treasurer*
Bruce E. Spivey
Thomas M. Aaberg
Michael A. Kass

EDITORIAL

Hydroxyamphetamine. A Good Drug Lost?

Ronald M. Burde and H. Stanley Thompson

In 1852, Bernard,[1] working with dogs, noticed an ipsilateral narrowing of the palpebral fissure and a decrease in the size of the pupil after cutting the cervical sympathetic nerve. But it was the case report of Horner[2] in 1869 that captured the imagination of the clinician. The combination of blepharoptosis, miosis, and anhidrosis was soon called Horner's syndrome and, at the time, was recognized as a sign of a lesion in the neck.

In 1932, Foerster and Gagel[3] introduced the sequential use of topical cocaine and epinephrine eyedrops to help make the diagnosis of Horner's syndrome and localize the site of the lesion. In 1971, Thompson and Mensher[4] remarked that cocaine failed to separate central from peripheral lesions because in both cases the affected pupil dilated poorly, and they emphasized the unreliability of the epinephrine test. As an alternative, they introduced the idea of first using topical cocaine to make the diagnosis of the sympathetic paresis, and then later instilling hydroxyamphetamine eyedrops to localize the site of the lesion.

Cocaine acts by preventing the re-uptake of norepinephrine, which under normal circumstances is released continuously from the sympathetic nerve endings in response to innervational tone. With re-uptake blocked by cocaine, the norepinephrine concentration at the neuromuscular junction increases until the dilator muscle is stimulated, and this stimulation dilates the pupil. A lesion anywhere in the sympathetic chain will decrease the tonic release of the norepinephrine, and this will lead to a poor pupillary dilation to topical cocaine. Because random drug testing for substance abuse is common, it is important to tell the patient that, after topical cocaine eyedrops are instilled, a urine test for cocaine is likely to be positive for at least 36 hours (100% at 24 hours; 53% at 36 hours).[5]

When doubt about the diagnosis of Horner's syndrome exists, the cocaine test is still the definitive procedure.[6,7] However, when the clinician is confident of the diagnosis—either as a result of looking for dilation lag with a video camera, or by comparing sweating or skin conductance on the two sides of the face—then the cocaine test can be skipped. There is no good substitute, however, for the localizing information provided by the hydroxyamphetamine test.

Hydroxyamphetamine is also an indirectly acting sympathomimetic agent, but it acts, like tyramine, by causing the release of norepinephrine from the postganglionic sympathetic nerve endings. These are the neurons that start in the superior cervical ganglion and travel up the carotid artery to the iris dilator muscle and to Müller's muscle. If a lesion has destroyed this third-order (peripheral) neuron, there will be no norepinephrine stores in the endings and no norepinephrine available for release, so there will be no mydriasis in response to hydroxyamphetamine. The response to the application of hydroxyamphetamine eyedrops localizes the site of the lesion: if the pupil dilates, then the third-order neuron is intact, and if it does not, the third-order neuron is damaged.

Thompson and Mensher[4] demonstrated in a patient with a presumed second-order neuron lesion (that is, the neuron that runs from the ciliospinal center of Budge in the spinal cord, over the pulmonary apex, to synapse in the superior cervical ganglion) that pretreatment with cocaine interfered with hydroxyamphetamine mydriasis. They recommended at least two days between drug applications. It is not known whether this precaution is always needed, but at present it adds further pressure in office practice to skip the cocaine test and go straight to the hydroxyamphetamine test.

In 1980, Maloney, Younge, and Moyer[8] showed that hydroxyamphetamine had a high sensitivity in identifying postganglionic lesions. In 1983, Van der Wiel and van Gijn[9] found hydroxyamphetamine to have a sensitivity of only 40% in identifying postganglionic lesions. Recently, Cremer and associates[10] demonstrated that although 1% hydroxyamphetamine is good at distinguishing postganglionic lesions from preganglionic lesions, a zone of equivocal response still remains. If the patient's pupillary inequality increases by only 0.5 mm after hydroxyamphetamine in both eyes, then no conclusions can be drawn from the test. Their data also show that, if hydroxyamphetamine eyedrops are used in a patient with a preganglionic lesion of the sympathetic pathway, the denervated pupil usually dilates more than the nonaffected pupil. Most neuro-ophthalmic textbooks[11-13] now recommend the sequential use of cocaine followed by hydroxyamphetamine, as suggested by Thompson and Mensher.[4]

Paredrine (hydroxyamphetamine hydrobromide 1%, Smith, Kline, & French) received Food and Drug Administration approval in 1938, and has been used as a mydriatic for more than 50 years. The recommendation in 1971[4] that it be used as a diagnostic preparation coincided with its general decline in popularity as a mydriatic agent, and in 1989, SmithKline Beecham discontinued the production of Paredrine. Gradually, as ophthalmologists and neurologists came to the bottom of their bottles of Paredrine and discovered that it was no longer available, SmithKline Beecham began to receive a flood of complaints, and neuro-ophthalmologists began to receive calls from colleagues asking where to get hydroxyamphetamine. At the present time, we do not have an answer.

In the 1970s, Paredrine was apparently banned from some countries on the grounds that it was an amphetamine and therefore might be sold on the black market as a recreational nose drop. If anyone ever used it in this way in expectation of some euphoric effect, they must have been badly disappointed. The structure of hydroxyamphetamine is apparently just sufficiently different from that of benzedrine to deprive it of its central euphoric effects. This was clearly demonstrated in the 1940s, when hydroxyamphetamine combined with a suspension of sulfathiazole was flushed in large quantities through inflamed paranasal sinuses without complaint of agitation or sleeplessness.

Tyramine hydrochloride might be substituted for hydroxyamphetamine, except that tyramine does not have hydroxyamphetamine's approval or its 50-year record as a gentle, safe, and dependable mydriatic, and far less clinical research has been done on tyramine as a diagnostic test in Horner's syndrome. Topical tyramine is reported to sting when applied.

Hydroxyamphetamine only lacks a supplier. It already has full Food and Drug Administration approval as a safe and effective mydriatic for human use (NDA 0004), which means that anyone is free to manufacture it and market it as a mydriatic, provided the solution is hydroxyamphetamine hydrobromide 1%, with appropriate preservatives added to the solution. All

the Food and Drug Administration requires is an "Abbreviated New Drug Application."

Is there an eyedrop manufacturer out there who would like to produce this solution in single dose packaging? There are many of us, neurologists as well as ophthalmologists, who feel the loss of hydroxyamphetamine 1% in our efforts to provide the best possible care for our patients, and we would be most grateful if this test were made available again. We suspect that clinicians would be willing to pay enough per dose to keep the operation out of the red.

This study was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

Reprint requests to Ronald M. Burde, M.D., Department of Ophthalmology, Albert Einstein College of Medicine, Montefiore Medical Center, 111 E. 210th St., Bronx, NY 10467-2490; or H. Stanley Thompson, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

References

1. Bernard, C.: Expérience sur la functions de la portion cèphalique du grand sympathique. C.R. Soc. Biol. (Paris) 4:155, 1852.

2. Horner, J. F.: Uber cure Foem von Ptosis Klin. Klin. Monatsbl. Augenheilkd. 7:193, 1869.

3. Foerster, O., and Gagel, O.: Die Vorderseitenstrang durchschneidung beum Menschen. Z. Neurol. Psychiatr. 138:1, 1932.

4. Thompson, H. S., and Mensher, J. H.: Adrenergic mydriasis in Horner's syndrome. Am. J. Ophthalmol. 72:472, 1971.

5. Bralliar, B. B., Skorf, B., and Owens, J. B.: Ophthalmic use of cocaine and the urine test for benzoylegonine. N. Engl. J. Med. 320:1757, 1989.

6. Kardon, R. H., Denison, C. E., Brown, C. K., and Thompson, H. S.: Critical evaluation of the cocaine test in the diagnosis of Horner's syndrome. Arch. Ophthalmol. 108:384, 1990.

7. Thompson, B. M., Corbett, J. J., Lines, L. B., and Thompson, H. S.: Pseudo-Horner's syndrome. Arch. Neurol. 39:108, 1982.

8. Maloney, W. F., Younge, B. R., and Moyer, N. J.: Evaluation of causes and accuracy of pharmacologic localization in Horner's syndrome. Am. J. Ophthalmol. 90:394, 1980.

9. Van der Wiel, H. L., and van Gijn, J.: Localization of Horner's syndrome. Use and limitations of the hydroxyamphetamine test. J. Neurol. Sci. 59:229, 1983.

10. Cremer, S. A., Thompson, H. S., Digre, K. B., and Kardon, R. H.: Hydroxyamphetamine mydriasis in Horner's syndrome. Am. J. Ophthalmol. 110:71, 1990.

11. Burde, R. M., Savino, P. J., and Trobe, J. D.: Clinical Decisions in Neuro-Ophthalmology. St. Louis, C. V. Mosby, 1985, pp. 232–234.

12. Miller, N. R.: Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4. Baltimore, Williams and Wilkins, 1985, pp. 507–511.

13. Glaser, J. S.: Neuro-Ophthalmology, ed. 2. Philadelphia, J. B. Lippincott, 1990, pp. 475–477.

LETTERS TO THE JOURNAL

Transesophageal Echocardiography for Detecting Mitral Valve Prolapse With Retinal Artery Occlusions

Craig M. Greven, M.D.,
Richard G. Weaver, M.D.,
William R. Harris, M.D.,
L. Earl Watts, M.D.,
and M. Madison Slusher, M.D.

Departments of Ophthalmology (C.M.G., R.G.W., M.M.S.) and Cardiology (L.E.W.), Wake Forest University Medical Center, and Graystone Ophthalmology Associates (W.R.H.).

Inquiries to Craig M. Greven, M.D., Department of Ophthalmology, Wake Forest University Eye Center, 300 S. Hawthorne Rd., Winston-Salem, NC 27103.

Mitral valve prolapse is the most common form of valvular heart disease.[1] Retinal arterial obstruction and central retinal venous occlusive disease have been associated with mitral valve prolapse.[2-4] The diagnosis of mitral valve prolapse can be made on clinical grounds, but echocardiography is required to confirm the diagnosis. We treated a patient with bilateral retinal arterial occlusion who had normal results of surface echocardiography on two occasions. However, transesophageal echocardiography, an improved method of imaging the cardiac valves, was able to document mitral valve prolapse in this patient.

A 35-year-old man had a three-week history of acute onset of an inferior scotoma in the right eye. Two years previously, the patient had developed an inferior scotoma in the left eye presumed to be secondary to a retinal vascular occlusion. Results of examination at that time were normal, including surface echocardiography. On examination, visual acuity was R.E.: 20/20 and L.E.: 20/20. Results of slit-lamp and pupillary examinations were normal. Small paracentral inferior scotomas were present bilaterally. Although results of retinal examination at this time were normal, fluorescein angiography of the right eye showed abrupt termination of the fluorescein and nonfilling of two superior branch retinal arterioles that corresponded exactly with the area of the scotoma (Figs. 1 and 2). Results of an examination and

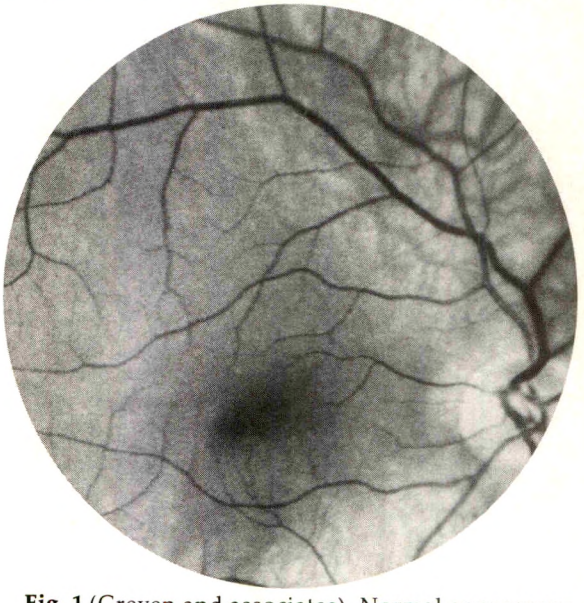


Fig. 1 (Greven and associates). Normal appearance of retinal vasculature and site of occlusion of the superotemporal artery.

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

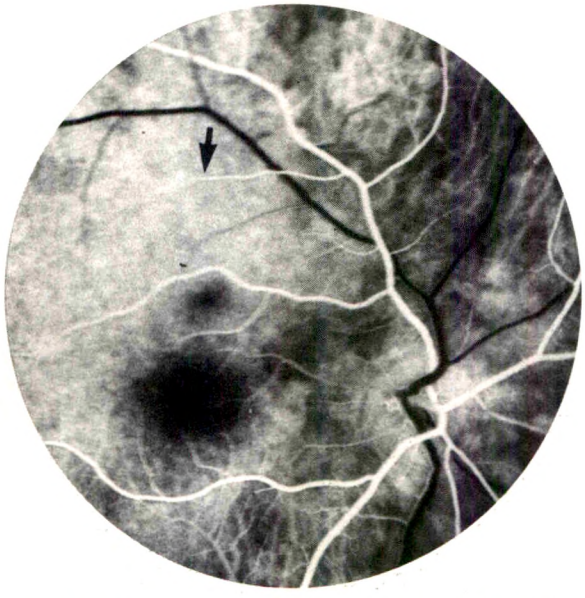


Fig. 2 (Greven and associates). Fluorescein angiogram of right eye showing abrupt termination of a branch of the superotemporal artery (arrow).

surface echocardiography were normal. However, transesophageal echocardiography disclosed myxomatous changes in the mitral valve with mitral valve prolapse. The patient was subsequently given aspirin and dipyridamole and has had no additional vascular occlusive events.

Transesophageal echocardiography has been shown to be better than surface echocardiography in detecting mitral valve prolapse and other cardiac abnormalities in young patients with cerebral ischemic events.[5] The transesophageal echo transducer is in closer proximity to the posterior heart structures, which allows the use of a high transducer frequency (5 mHz) to improve the resolution of the posterior heart structures as well as the mitral valve, left atrium, and aortic valve. The findings in our case demonstrate that this technologic advance was better than traditional transthoracic echocardiography in documenting the source of the retinal arterial occlusion. Ophthalmologists should be aware of transesophageal echocardiography and consider this improved diagnostic modality for patients with unexplained retinal artery occlusions, even with normal results of surface echocardiography.

References

1. Rackley, C. E.: Valvular heart disease. In Wyngaarden, J. B., and Smith, L. H. (eds.): Cecil Textbook of Medicine, ed. 18. Philadelphia, W. B. Saunders, 1988, p. 340.
2. Woldoff, H. S., Gerber, M., Desser, K. B., and Benchimol, A.: Retinal vascular lesions in two patients with mitral valve leaflets. Am. J. Ophthalmol. 79:382, 1975.
3. Caltrider, N. D., Irvine, A. R., Kline, H. J., and Rosenblatt, A.: Retinal emboli in patients with mitral valve prolapse. Am. J. Ophthalmol. 90:534, 1980.
4. Gonder, J. R., Magargal, L. E., Walsh, P. N., Rao, K., and Denenberg, B. E.: Central retinal vein obstruction associated with mitral valve prolapse. Can. J. Ophthalmol. 18:220, 1983.
5. Zenker, G., Erbel, R., Kramer, G., Mohr-Kahaly, S., Drexler, M., Harnoncourt, K., and Meyer, J.: Transesophageal two-dimensional echocardiography in young patients with cerebral ischemic events. Stroke 19:345, 1988.

Use of Transesophageal Echocardiography for Detection of a Likely Source of Embolization to the Central Retinal Artery

Robert A. Wiznia, M.D., and W. Neil Pearson, M.D.

Departments of Ophthalmology and Visual Science (R.A.W.) and Internal Medicine (W.N.P.), Yale University School of Medicine.

Inquiries to Robert A. Wiznia, M.D., 850 Howard Ave., New Haven, CT 06519-1193.

Transesophageal echocardiography provides a substantially clearer view of cardiac structures than does transthoracic echocardiography. Transesophageal echocardiography uses a 5-MHz ultrasound transducer attached to the distal tip of a standard flexible gastroscope. By placing the transducer in the esophagus directly behind the heart, the technique avoids the tissue, bone, and air interfaces that attenuate transthoracic echocardiography ultrasound images.[1] We used this technique to detect a likely cardiac source of embolization to the central retinal artery, which was not evident with transthoracic echocardiography.

A 47-year-old woman was examined approximately two hours after she noted sudden, severe loss of vision in her left eye on Dec. 16, 1989. Visual acuity was R.E.: 20/25 and L.E.: light perception with poor projection. Intraocular pressure by applanation tonometry was 19 mm Hg in each eye. Results of examination of the right eye were unremarkable. Examination of the left eye disclosed a cherry-red spot in the center of the macula surrounded by white translucent retina in the posterior pole. The retinal arteries were patent, although they were slightly narrower than those in the right eye. No emboli were noted. Ophthalmodynamometry disclosed an ophthalmic artery pressure of 50 mm Hg in each eye.

The patient's medical history was noncontributory, and results of the general physical examination were unremarkable. Laboratory and diagnostic tests included the following values: white blood cell count, 8,700; hemoglobin, 149 g/l; hematocrit, 42.5%; erythrocyte sedimentation rate, 10 mm/hr; prothrombin time, 11.0 seconds; partial thromboplastin time, 29.7 seconds; normal serum protein electrophoresis level; negative antinuclear antibody test; negative VDRL test; and negative fluorescent treponemal antibody absorption test. A Doppler ultrasonographic study of the carotid arteries was unremarkable.

Results of transthoracic echocardiography were normal. Transesophageal echocardiography, however, disclosed a 2.5-cm interatrial septal aneurysm with a small thrombus adherent to the left atrial side. We believed this to be the likely source for the embolus that led to the left central retinal artery occlusion.

The patient was given 300 mg of aspirin daily and has had no additional symptoms or signs of an embolic event. The left optic disk developed generalized pallor, and the sensory retina, especially in the macula, had an ischemic appearance. At the most recent examination on May 15, 1990, visual acuity was L.E.: 2/400.

Daniel and associates[2] demonstrated that tranesophageal echocardiography leads to a significant improvement in the identification of potential cardiac sources for arterial embolism associated with cerebral ischemic events when compared to results using transthoracic echocardiography. The findings in our patient demonstrate the value of transesophageal echocardiography for the detection of a potential source for an unexplained arterial embolism causing a central retinal artery occlusion. Physicians should consider the use of this technique when medical examination, including Doppler ultrasonography and transthoracic echocardiography, do not detect the origin of a central retinal artery occlusion.

References

1. Schnittger, I.: Clinical applications of transesophageal echocardiography. Pract. Cardiol. 16:52, 1990.

2. Daniel, W. G., Angermann, R. E., Erbel, R., Hanrath, P., Sabino, I., Kasper, W., and Visser, E. E.: Transesophageal echocardiography in patients with cerebral ischemic events and arterial embolism. A European multicenter study. Circulation 80:II–473, 1989.

Follicular Conjunctivitis Associated With Apraclonidine

Mark Wilkerson, M.D., Richard A. Lewis, M.D., and M. Bruce Shields, M.D.

Duke University Eye Center (M.W., M.B.S.), and Department of Ophthalmology, University of California, Davis (R.A.L.).

Inquiries to M. Bruce Shields, M.D., Duke University Medical Center, Box 3802, Durham, NC 27710.

Apraclonidine hydrochloride 1% ophthalmic solution has been demonstrated to decrease the magnitude and prevalence of intraocular pressure increases significantly after anterior segment laser procedures.[1,2] Other studies have examined the efficacy and safety of topical apraclonidine therapy for glaucoma.[3,4] Eyelid retraction, conjunctival blanching, and dryness of the mouth and nose are among the more common side effects reported with this agent.[3,4] We treated two patients with follicular conjunctivitis observed during a clinical trial with apraclonidine hydrochloride.

The clinical trial involved the adjunctive use of 0.06%, 0.125%, or 0.25% apraclonidine hydrochloride added to timolol maleate 0.5% in patients with primary open-angle glaucoma. Each drug was used twice a day. Two patients

developed follicular conjunctivitis similar to that noted with topical epinephrine compounds.

Case 1

A 34-year-old white man had been using timolol maleate 0.5% twice daily in both eyes for primary open-angle glaucoma. The patient entered the clinical trial, and apraclonidine 0.125% in each eye twice daily was prescribed in conjunction with the timolol therapy. One month later, he had itchy, irritated eyes. A bilateral, mixed papillary and follicular conjunctivitis was observed. Apraclonidine was discontinued and timolol was continued. The patient's signs and symptoms subsequently resolved. The previous regimen of apraclonidine and timolol was then restarted. Two weeks later, the same clinical course recurred. With discontinuation of apraclonidine hydrochloride, the conjunctivitis again resolved.

Case 2

A 39-year-old white man who was taking timolol maleate 0.5% in each eye twice daily for primary open-angle glaucoma entered the study and began taking apraclonidine hydrochloride 0.06% in each eye. Because of inadequate control of intraocular pressure, the regimen was advanced to 0.125% and later 0.25% apraclonidine in accordance with the study protocol. Approximately seven weeks after initiating apraclonidine therapy, moderate conjunctival injection of both eyes was noted. Intraocular pressure remained uncontrolled with the 0.25% concentration, and a unilateral trial to test for efficacy was undertaken. Apraclonidine was discontinued in only the right eye, and timolol was maintained in each eye. The patient returned six weeks later with redness and itching of the left eye. A prominent follicular conjunctivitis was noted in the left eye only. There was no evidence of an infectious origin. After stopping only the apraclonidine, the signs and symptoms resolved.

Toxic and hypersensitivity reactions of the conjunctiva are not uncommon side effects of topical ophthalmic medications. The relationship of follicular conjunctivitis and topical epinephrine compounds is well recognized.[5] The findings in these two patients suggest that the alpha-2 agonist, apraclonidine, may cause a similar inflammatory response. Whether this is a property of apraclonidine hydrochloride solution itself or of timolol and apraclonidine used concomitantly is unclear. The apraclonidine vehicle consists of 0.01% benzalkonium chloride as a preservative and the inactive ingredients sodium chloride, sodium acetate, sodium hydroxide, hydrochloric acid, and purified water. Apraclonidine itself seems the most likely component to have a role in this reaction. The other ingredients are common to other topical ophthalmic medications that have not been reported to cause follicular conjunctivitis. This response may be caused by a toxic effect or a hypersensitivity reaction. In either case, physicians should be aware of the potential for inducing follicular conjunctivitis with long-term topical apraclonidine hydrochloride therapy.

References

1. Robin, A. L., Pollack, I. P., House, B., and Enger, C.: Effects of ALO 2145 on IOP following argon laser trabeculoplasty. Arch. Ophthalmol. 105:646, 1987.

2. Brown, R. H., Stewart, R. H., Lynch, M. G., Crandall, A. S., Mandell, A. I., Wilensky, J. T., Schwartz, A. L., Gaasterland, D. E., DeFaller, J. M., and Higginbotham, E. J.: ALO 2145 reduces the intraocular pressure elevation after anterior segment laser surgery. Ophthalmology 95:378, 1988.

3. Morrison, J. C., and Robin, A. L.: Adjunctive glaucoma therapy. A comparison of apraclonidine to dipivefrin when added to timolol maleate. Ophthalmology 96:3, 1989.

4. Abrams, D. A., Robin, A. L., Pollack, I. P., DeFaller, J. M., and DeSantis, L.: The safety and efficacy of topical 1% ALO 2145 (p-aminoclonidine hydrochloride) in normal volunteers. Arch. Ophthalmol. 105:1205, 1987.

5. Theodore, J., and Leibowitz, H. M.: External ocular toxicity of dipivalyl epinephrine. Am. J. Ophthalmol. 88:1013, 1979.

The Importance of the Schirmer Test With Nasal Stimulation

Kazuo Tsubota, M.D.

Department of Ophthalmology, Tokyo Dental College, and Keio University School of Medicine.

Inquiries to Kazuo Tsubota, M.D., Department of Ophthalmology, Tokyo Dental College, 7-1 Sugano 6 chome, Ichikawa-shi, Chiba, Japan 272.

The Schirmer test, used for the detection of dry eye conditions, is often used in clinics

because it is relatively quick and easy to administer. Since the original Schirmer test does not use anesthesia, it causes irritation in patients. Therefore, the modified technique of the Schirmer test with topical anesthesia is preferred. With or without anesthesia, the reflex tear is capable of altering the results of the Schirmer test, which makes it highly unstable.[1]

To obtain the maximum amount of reflex tears, several methods have been advocated, such as lemon and nasal stimulation. Although these stimulation methods have been reported,[2] they are not being used in clinics because the importance of this test has not been emphasized, and the procedure is complicated. I developed a quick and easy method for obtaining maximal lacrimal reflex.

A patient was instructed to sit back and relax on a chair with a high back. The purpose of this procedure, to maximize tearing, was then explained. A small cotton-tipped applicator was then inserted into the nose until the tip of the applicator reached the nasal membrane of the ethmoid sinus. (If the examiner is not familiar with the anatomy of the nasal cavity, the procedure is performed with a nasal opener and an indirect ophthalmoscope [Figure]. With some experience, it becomes easier to insert the cotton-tipped applicator without direct observation.) The Schirmer test was then performed, regardless of whether or not the patient noticed the tearing.

Patients with Sjögren's syndrome (seven women; mean age, 56.0 ± 6.4 years), patients with keratoconjunctivitis sicca and increased autoantibody levels, such as antinuclear antibody or rheumatoid arthritis factor (eight women and two men; mean age, 54.2 ± 8.5 years), and patients with keratoconjunctivitis sicca without any systemic abnormalities (seven women and five men; mean age, 48.9 ± 14.1 years) were recruited for this study. Using topical anesthesia the Schirmer test was performed first, and then the cotton-tipped applicator was inserted into the nasal cavity on the side with less tearing. The Schirmer test was then performed again, and the results were compared. The patients did not have nasal bleeding or severe pain. Some of the patients asked to take the test again because the tearing was a relief to them.

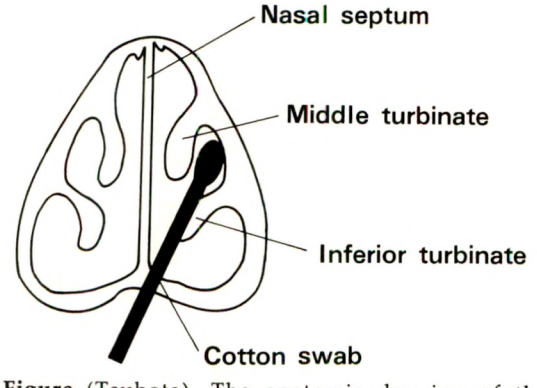


Figure (Tsubota). The anatomic drawing of the nasal cavity and the cotton-tipped applicator. The ethmoid meatus (arrow) is touched gently with the cotton-tipped applicator.

Patients with Sjögren's syndrome, patients with keratoconjunctivitis sicca and increased autoantibody levels, and patients with keratoconjunctivitis sicca alone had Schirmer test results of 3.6 ± 3.9 mm, 1.9 ± 1.7 mm, and 2.0 ± 2.0 mm in the worse eyes, respectively. In the better eyes, the results were 5.3 ± 4.5 mm, 2.6 ± 2.4 mm, and 4.8 ± 8.3 mm, respectively. There were no statistical differences among the three groups in the worse or better eyes. After nasal stimulation to the worse eyes, the results were 2.1 ± 2.9 mm, 18.1 ± 11.9 mm ($P < .01$), and 24.6 ± 12.0 mm ($P < .001$) in stimulated eyes, respectively. The results were 0.9 ± 1.4 mm, 4.8 ± 3.6 mm, and 6.0 ± 3.9 mm in the eyes opposite nasal stimulation, respectively (not statistically significant).

Two findings became apparent through this test. The simple Schirmer test could not differentiate patients with Sjögren's syndrome from the patients who did not have Sjögren's syndrome. Nasal stimulation could increase the tearing dramatically in patients who did not have Sjögren's syndrome, whereas no increase was observed in patients with Sjögren's syndrome. Thus, nasal stimulation can differentiate between the two conditions.

In patients with Sjögren's syndrome, the lacrimal glands are destroyed by lymphocyte infiltration[3,4] and are not expected to respond to the stimulation. My findings may suggest that the patients with keratoconjunctivitis sicca who do not have Sjögren's syndrome have normal capability of reflex tearing but less basal tearing without stimulation. Since these patients are expected to have normal morphologic structure of the lacrimal gland, keratoconjunctivitis sicca may not be a disease of the lacrimal gland, but it may be caused by the decreased sensitivity of the cornea and conjunctiva or by the functional

stenosis of the lacrimal duct as seen in contact lens wearers or at the beginning of the Sjögren's syndrome. This nasal stimulation is a safe and easy procedure with less discomfort for the patients. I recommend this test be performed to examine the maximal ability of tearing in patients, which can help in the differential diagnosis of patients with keratoconjunctivitis sicca.

References

1. Goren, M. B., and Goren, S. B.: Diagnostic tests in patients with symptoms of keratoconjunctivitis sicca. Am. J. Ophthalmol. 106:570, 1988.

2. Lamberts, D. W.: Dry eyes. In Smolin, G., and Thoft, R. A. (eds.): The Cornea. Boston, Little, Brown and Company, 1983, p. 293.

3. Adamson, T. C., Fox, R. I., Frisman, D. M., and Howell, F. V.: Immunohistologic analysis of lymphoid infiltrates in primary Sjögren's syndrome using monoclonal antibodies. J. Immunol. 130:204, 1983.

4. Belfort, R., and Mendes, N. F.: T and B lymphocytes in the human conjunctiva and lacrimal gland. In Silverstein, A., and O'Connor, R. G. (eds.): Immunology and Immunopathology of the Eye. New York, Masson Publishing, 1979, p. 287.

Discoid Lupus Erythematosus of the Eyelid Complicated by Wound Dehiscence

Rhondi S. Meiusi, M.D., J. Douglas Cameron, M.D., Edward J. Holland, M.D., and C. Gail Summers, M.D.

Department of Ophthalmology, University of Minnesota.

Inquiries to Rhondi S. Meiusi, M.D., Department of Ophthalmology, University of Minnesota, Box 493 UMHC, 516 Delaware St. S.E., Minneapolis, MN 55455.

Eyelid involvement is rarely reported as the sole manifestation of discoid lupus erythematosus.[1-5] The differential diagnosis includes blepharitis, contact dermatitis, lymphocytic infiltrates, and sebaceous cell carcinoma. Early diagnosis and treatment are desirable to prevent eyelid dysfunction. We treated a patient in whom a full-thickness eyelid biopsy was complicated by multiple episodes of wound dehiscence secondary to the chronic inflammation of a discoid lupus lesion.

A 29-year-old man had a four-year history of an erythematous, indurated lesion of the left upper eyelid. The patient was in good general health. The eyelid was treated with topical corticosteroids without improvement.

Ocular examination disclosed a well-demarcated, erythematous, indurated, scaling lesion involving 90% of the left upper eyelid and eyelid margin (Fig. 1). Madarosis was seen along the medial one half of the eyelid. The palpebral conjunctiva was not inflamed. Results of the remainder of the ophthalmic, dermatologic, and physical examinations were normal.

Since an eyelid carcinoma was suspected, a full-thickness wedge biopsy of the left upper eyelid was performed at the lateral border of madarosis. Pathologic examination disclosed hyperkeratosis with mild keratin plugging, hydropic degeneration of the basal epidermal layer, and moderate lymphocytic infiltrate within the dermis, particularly around cutaneous appendages. Direct immunofluorescence studies disclosed deposition of IgG, IgA, and C3 along the dermal-epidermal junction, a finding consistent with lupus erythematosus (Fig. 2). Results of laboratory studies were normal.

The original surgical incision was closed with interrupted polyglactin sutures in the tarsus and subcutaneous tissues, without tension on the wound. Nine days postoperatively, the patient had total wound dehiscence. Persistent inflammation was present without evidence of infection. The margins of the wound were freshened, and the dehiscence was repaired by layered closure combined with a lateral canthotomy. Six days postoperatively, the patient

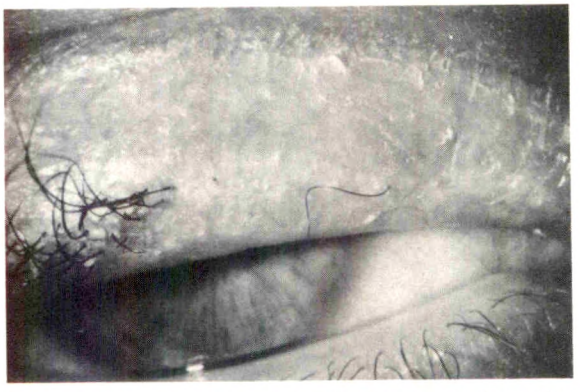


Fig. 1 (Meiusi and associates). Demarcated, scaling lesion with madarosis of the left upper eyelid.

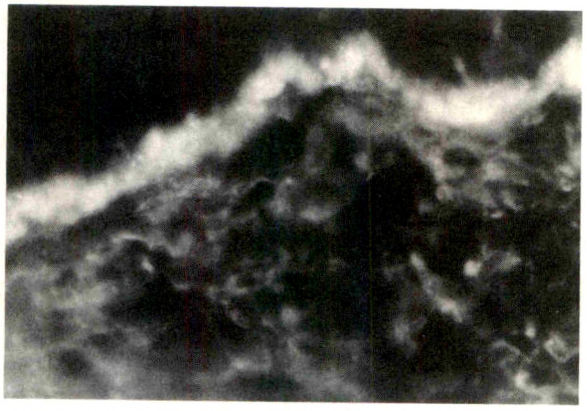


Fig. 2 (Meiusi and associates). Granular deposition of IgG along the dermal-epidermal junction.

again had wound dehiscence. Repair was then performed with multiple horizontal mattress sutures placed over sponge bolsters after a flap had been advanced from the lateral canthus. Surgical repair was supplemented with intralesional injection of dexamethasone. The wound healed without additional complications, and follow-up examination six months postoperatively showed an intact eyelid with less induration and erythema.

In rare cases, eyelid involvement may be the sole manifestation of discoid lupus erythematosus. Recognition of the possibility of this entity is important before surgical manipulation, as poor wound healing may occur. Diagnosis is confirmed by immunofluorescence studies of biopsy specimens of the lesions. Treatment with antimalarials is usually effective when persistent eyelid inflammation occurs.

References

1. Kearns, W., Wood, W., and Marchese, A.: Chronic cutaneous lupus involving the eyelid. Ann. Ophthalmol. 14:1009, 1982.

2. Huey, C., Jakobiec, F. A., Iwamoto, T., Kennedy, R., Farmer, E. R., and Green, R.: Discoid lupus erythematosus of the eyelids. Ophthalmology 90:1389, 1983.

3. Donzis, P. B., Insler, M. S., Buntin, D. M., and Gately, L. E.: Discoid lupus erythematosus involving the eyelids. Am. J. Ophthalmol. 98:32, 1984.

4. Ziv, R., Schewach-Millet, M., and Trau, H.: Discoid lupus erythematosus of the eyelids. J. Am. Acad. Dermatol. 15:112, 1986.

5. Tosti, A., Tosti, G., and Giovannini, A.: Discoid lupus erythematosus solely involving the eyelids. Report of three cases. J. Am. Acad. Dermatol. 16:1259, 1987.

Hepatic Cirrhosis as a Doubtful Cause of Eyelid Retraction

George B. Bartley, M.D., and Colum A. Gorman, M.D.

Departments of Ophthalmology (G.B.B.) and Endocrinology (C.A.G.), Mayo Clinic and Mayo Foundation.

Inquiries to George B. Bartley, M.D., Department of Ophthalmology, Mayo Clinic, Rochester, MN 55905.

Eyelid retraction is most commonly caused by Graves' disease and is a sensitive and specific sign of this systemic disorder. Most textbooks and reviews that discuss dysthyroid ophthalmopathy include hepatic cirrhosis in the differential diagnosis for eyelid retraction.[1] The origin of this supposition is a report in 1962 from our institution that described eyelid retraction or eyelid lag in association with liver cirrhosis.[2] Graves' ophthalmopathy was considered as a possible cause of the ocular signs, but the authors stated that "thyroid disease could not be substantiated in any patient on the basis of history, physical examination, or tests of thyroid function." The authors indicated that "the mechanism of these eye signs in cirrhosis . . . remains obscure." Because we also could not explain the pathophysiologic characteristics of eyelid retraction presumably secondary to cirrhosis and because we had not observed true eyelid retraction in such a clinical setting, we reviewed the original report in hopes of clarifying this association.

Summerskill and Molnar[2] studied 110 patients with hepatic cirrhosis and documented



Fig. 1 (Bartley and Gorman). Case 1 of Summerskill and Molnar.[2] Patient with cirrhosis after hepatitis and probable autoimmune thyroid disease.

eyelid retraction or eyelid lag in 13 patients. Photographs of two of the 13 patients (Cases 1 and 12) were included in the report, and the medical records of these two patients could be traced through the sections of publications and photography at our institution. The remaining 11 patients could not be identified.

In the patient described in Case 1, the thyroid gland was noted in the medical record to be diffusely palpable and questionably of normal size. The only laboratory test result relating to thyroid function was a protein-bound iodine level of 2.8 μg/dl (normal, 3.5 to 7.5 μg/dl). This result is suggestive of autoimmune thyroid disease, and the clinical features of eyelid retraction, esotropia (possibly from a restricted right medial rectus muscle), and conjunctival injection over the horizontal rectus muscle insertions are consistent with Graves' ophthalmopathy (Fig. 1). The data available are inadequate by current endocrinologic standards to exclude Graves' disease.

Review of the record of the patient described in Case 12 showed that thyrotoxicosis had been diagnosed before examination at our institution and had been treated with methimazole and radioactive iodine. The patient's eyelid retraction, proptosis, and eyelid fullness are virtually pathognomonic for Graves' ophthalmopathy (Fig. 2).

We conclude from review of the records of these two patients that their eyelid retraction was secondary to dysthyroid ophthalmopathy and not to hepatic cirrhosis as had been conjectured in the original report. In our experience, true eyelid retraction (that is, not related to an obvious secondary cause such as proptosis, aberrant oculomotor nerve regeneration or synkinesis, midbrain disease, or previous eyelid surgery) is an extremely specific indicator of thyroid dysfunction.[3] Contemporary laboratory tests are much more sophisticated and sensitive than those available 30 years ago, and an abnormality of thyroid regulation can be identified in nearly every patient with true eyelid retraction.

It is possible that chronic liver disease could result in a staring appearance if severe ascites results in vascular congestion and proptosis. We are skeptical, however, that hepatic cirrhosis directly affects Müller's muscle or the levator palpebrae superioris muscle to cause true eyelid retraction.

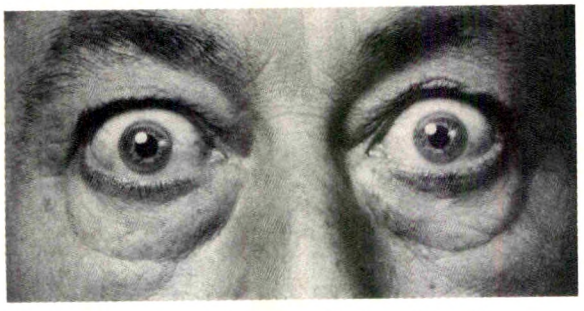


Fig. 2 (Bartley and Gorman). Case 12 of Summerskill and Molnar.[2] Patient with alcoholic cirrhosis and known history of thyrotoxicosis. Reprinted by permission of The New England Journal of Medicine, 266:1244, 1962.

References

1. Waller, R. R., Samples, J. R., and Yeatts, R. P.: Eyelid malpositions in Graves' ophthalmopathy. In Gorman, C. A., Waller, R. R., and Dyer, J. A. (eds.): The Eye and Orbit in Thyroid Disease. New York, Raven Press, 1984, p. 267.

2. Summerskill, W. H. J., and Molnar, G. D.: Eye signs in hepatic cirrhosis. N. Engl. J. Med. 266:1244, 1962.

3. Bahn, R. S., Garrity, J. A., Bartley, G. B., and Gorman, C. A.: Diagnostic evaluation of Graves' ophthalmopathy. Endocrinol. Metab. Clin. North Am. 17:527, 1988.

Flotation Devices to Facilitate Amblyopia Therapy

Henry D. Hacker, M.D., and Mary O'Hara, M.D.

Ophthalmology Service, Department of Surgery, Brooke Army Medical Center. The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Inquiries to CPT. Henry Hacker, M.C., U.S.A., Ophthalmology Service, Department of Surgery, Brooke Army Medical Center, Ft. Sam Houston, TX 78234-6200.

Compliance with occlusion therapy for amblyopia can be difficult. We developed an approach to facilitate patching of the eyes of reluctant infants during treatment of amblyopia. Children who have dense amblyopia are often unsettled when the fellow eye is occluded. Even small infants are able to remove the

cloth patch from the fellow eye many times each day. This not only frustrates the parents but can also produce significant periocular skin irritation, which forces interruption of treatment. In the quest for restoration of useful vision, various methods have been described that are directed at preventing the child from reaching up to the eye and taking off the patch.

Techniques used to restrict upper extremity motion include wrapping magazines around the arms, using plastic tubing, and even using custom-made restraints from the orthopedic service for particularly difficult cases.[1,2] Many parents find these approaches unacceptable or difficult to apply, further complicating the treatment of amblyopia. Recently, the mother of a child with unilateral aphakia noted that poolside flotation devices placed at the elbow prevented her son from removing his orthoptic patch (Figure). We have since found this approach extremely effective whenever parents have difficulty in getting their infant to comply with an occlusion regimen. Additionally, we have noted that use of flotation devices is particularly valuable during initiation of treatment or to ensure compliance in patients who require prolonged treatment. Flotation devices are light and well accepted both by the infant and the parents. The devices sufficiently restrict arm extension to prevent patch removal while providing adequate range of motion for other tasks.

At the age of 12 to 16 months, many children are able to circumvent this method, which necessitates other forms of restraint. Nevertheless, we anticipate this approach will provide ophthalmologists with a helpful adjunct in amblyopia therapy.

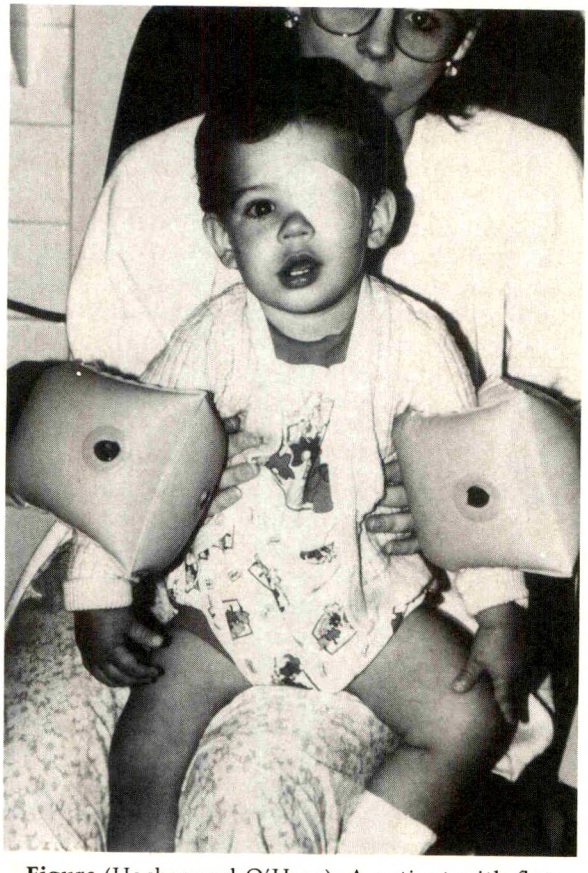


Figure (Hacker and O'Hara). A patient with flotation devices positioned around the arm.

References

1. Kushner, B. J.: Functional amblyopia. A purely practical pediatric patching protocol. In Reinecke, R. D. (ed.): Ophthalmology Annual. New York, Raven Press, 1988, p. 188.

2. Greenwald, M. J., and Parks, M. M.: Treatment of amblyopia. In Tasman, W. (ed.): Duane's Clinical Ophthalmology. Philadelphia, J. B. Lippincott, 1989, pp. 1–3.

Retinal Pigment Epitheliopathy in Acute Leukemia

Frank D. Verbraak, M.D., Wouter van den Berg, M.D., and Pierre J. M. Bos, M.D.

Department of Ophthalmology, University of Amsterdam.

Inquiries to Frank D. Verbraak, M.D., Department of Ophthalmology, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

In histopathologic studies, ocular involvement in patients with leukemia has been estimated to occur in 50% of cases.[1] Retinal pigment epitheliopathy in acute leukemia was described by Clayman and associates,[2] Jakobiec and Behrens,[3] and Inkeles and Friedman.[4] We treated a patient with retinal pigment epitheliopathy associated with acute lymphoblastic leukemia.

In 1987, acute lymphoblastic leukemia was diagnosed in a 6-year-old boy. The patient was treated with chemotherapy according to proto-



Fig. 1 (Verbraak, van den Berg, and Bos). Posterior pole showing yellow-white lesions in a reticular pattern at the level of the pigment epithelium.

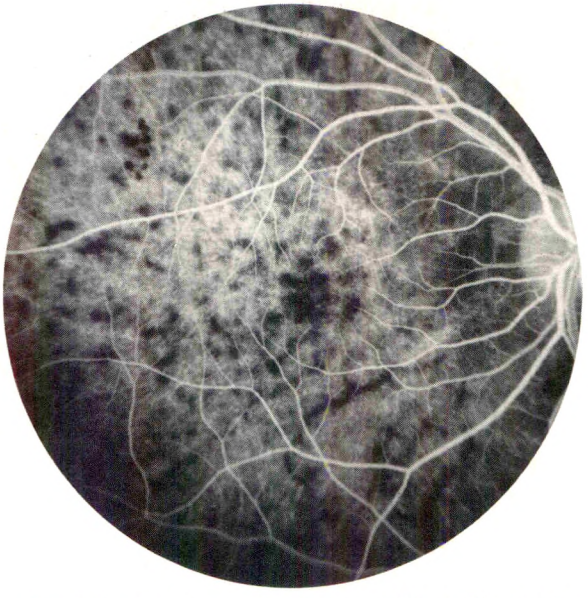


Fig. 2 (Verbraak, van den Berg, and Bos). Fluorescein angiogram of the posterior pole of the right eye showing early hyperfluorescence in a pattern corresponding to the yellow-white lesions seen on ophthalmoscopy.

col, and the leukemia went into remission. In June 1989, a relapse was treated successfully. In this period, loss of vision of the right eye was noted, but the patient was not examined by an ophthalmologist. Three months later, the patient was referred to our department.

Visual acuity was R.E.: counting fingers and L.E.: 16/20. The adnexa and anterior segments were normal. Cells were noted in the vitreous of the right eye. Fundus examination of the right eye showed a peculiar pigment epithelial alteration throughout the posterior pole, including the fovea, and extending to the midperiphery. It consisted of a reticular pattern of yellow-white lesions surrounding areas of retina with a normal aspect (Fig. 1). The left eye was normal. Fluorescein angiography of the right eye showed early hyperfluorescence in a reticular pattern corresponding with the yellow-white lesions seen with ophthalmoscopy, without leakage or staining (Fig. 2). Electro-oculography showed a normal light peak/dark trough ratio in both eyes. Electroretinography showed photopic and scotopic lowered a- and b-potentials, prolonged implicit times in the right eye, and normal values in the left eye. No therapeutic measures were taken. After five months, visual acuity in the right eye improved to 4/20. On ophthalmoscopy, a sharper demarcation of the reticular pattern of yellow-white lesions was visible, without extension of involved areas. Electroretinography showed all values returning to normal.

The ophthalmoscopic findings in this patient, and of the four patients previously described,[2-4] show similarity in the location and the extent of the pigment epithelial alteration. Histopathologic examination by Clayman and associates[2] and Inkeles and Friedman[4] demonstrated destruction and hyperplasia accompanied by leukemic infiltration of the retina and the choroid. Jakobiec and Behrens[3] suggested an irritation of the pigment epithelium, secondary to leukemic infiltration of the choroid, resembling the course seen in acute placoid multifocal posterior pigment epitheliopathy. The electrophysiologic findings in our patient support this suggestion. A normal electro-oculogram with an abnormal electroretinogram and the electroretinogram returning to normal with improvement of visual acuity are also seen in acute placoid multifocal posterior pigment epitheliopathy.[5]

The variability in the severity of the damage to the pigment epithelium, ranging from large areas of destruction[2,4] to the still functional intact epithelium in our patient, and the frequent occurrence of choroidal infiltration in patients with leukemia[1] makes it likely that more cases of leukemic pigment epitheliopathy

could be identified with the help of a combination of ophthalmoscopy, fluorescein angiography, and electrophysiologic examination, even in the absence of visual complaints.

References

1. Leonardy, N. J., Rupani, M., Dent, G., and Klintworth, G. K.: Analysis of 135 autopsy eyes for ocular involvement in leukemia. Am. J. Ophthalmol. 109:436, 1990.

2. Clayman, H. M., Flynn, J. T., Koch, K., and Israel, C.: Retinal pigment epithelial abnormalities in leukemic disease. Am. J. Ophthalmol. 74:416, 1972.

3. Jakobiec, F., and Behrens, F.: Leukemic retinal pigment epitheliopathy. J. Pediatr. Ophthalmol. 12:10, 1975.

4. Inkeles, D. M., and Friedman, A. H.: Retinal pigment epithelial degeneration, partial retinal atrophy and macular hole in acute lymphocytic leukemia. Graefes Arch. Clin. Exp. Ophthalmol. 194:253, 1975.

5. Gass, J. D. M: Acute posterior multifocal placoid pigment epitheliopathy. In Gass, J. D. M (ed.): Stereoscopic Atlas of Macular Diseases. Diagnosis and Treatment, ed. 3. St. Louis, C. V. Mosby, 1987, pp. 504–508.

Metastatic Renal Cell Carcinoma of the Iris Manifesting as an Intrastromal Iris Cyst

Scott L. Portnoy, M.D., Robert C. Arffa, M.D., Bruce L. Johnson, M.D., and Irwin S. Terner, M.D.

Eye and Ear Institute of Pittsburgh, University of Pittsburgh School of Medicine.

Inquiries to Robert C. Arffa, M.D., Eye and Ear Institute of Pittsburgh, 203 Lothrop St., Pittsburgh, PA 15213.

Metastatic tumors to the iris are often not clinically diagnosed unless there is a history or clinical evidence of cancer elsewhere in the body. They may be suspected based on the relatively rapid growth of white-pink masses on the iris surface or acute iridocyclitis unresponsive to standard therapy. We treated a patient who had an intrastromal cystic-appearing iris mass caused by metastatic renal cell carcinoma.

A 65-year-old man had decreased vision in the left eye. Sixteen months before this manifestation, the patient had undergone uneventful cataract extraction with implantation of a posterior chamber intraocular lens. He was otherwise in good health, although he smoked two packs of cigarettes daily. Best-corrected visual acuity was R.E.: 20/60 and L.E.: 20/200. Intraocular pressure was R.E.: 18 mm Hg and L.E.: 42 mm Hg. The left anterior chamber contained mild cell and flare. Fine iris neovascularization was present along the pupillary border. There was a smooth dome-shaped elevation of the superior portion of the iris, which extended from the 11 o'clock to the 12 o'clock meridian (Fig. 1). There was a pink-white mass beneath the surface of the iris, which transilluminated. On gonioscopic examination, gray-white material, similar to Elschnig's pearls, was noted posterior to the iris mass. Peripheral anterior synechiae were present over one third of the angle. Results of ophthalmoscopy were normal, and results of a chest x-ray were normal. Results of laboratory tests for complete blood cell count, erythrocyte sedimentation rate, carcinoembryonic antigen assay, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, calcium, blood urea nitrogen and creatinine, and noninvasive carotid testing were within normal limits.

Results of the examination were consistent with an epithelial implantation cyst, secondary to the previous cataract surgery; however, this did not account for the associated iris neovascularization. Adenoma of the nonpigmented ciliary epithelium, metastatic carcinoma, and leiomyoma were considered as other possibilities. Two months later, the iris lesion was larger, intraocular pressure became more difficult to

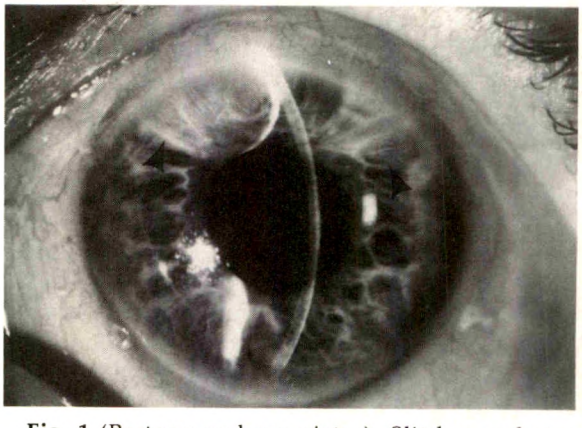


Fig. 1 (Portnoy and associates). Slit-lamp photograph of superior iris mass (arrows).

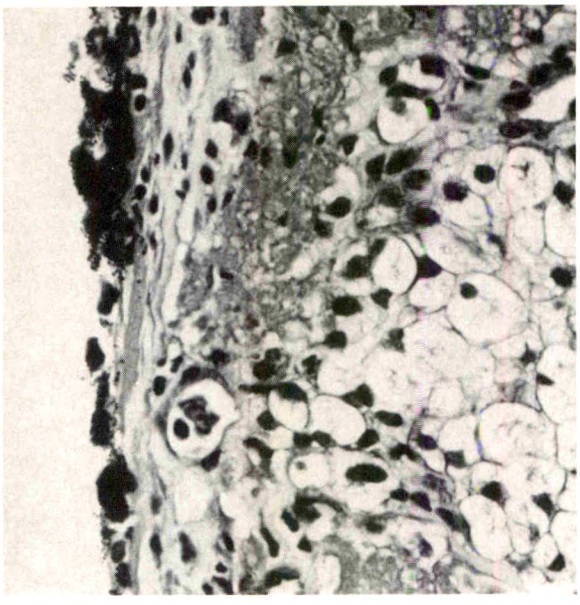


Fig. 2 (Portnoy and associates). Light microscopic appearance of iris tumor, displaying sheets of polyhedral-shaped cells with clear cytoplasm infiltrating the iris stroma. Remnants of iris pigment epithelium are seen on the left (hematoxylin and eosin, × 250).

control, and the lesion was excised by means of a superior sector iridectomy. Pathologic examination disclosed a finely vascularized globular gelatinous mass measuring 6 × 5 × 4 mm. Microscopically, the mass consisted of sheets of large rounded or polygonal-shaped cells having abundant clear cytoplasm rich in glycogen and lacking mucus (Fig. 2). The histologic appearance was consistent with a metastatic renal clear cell carcinoma. A computed axial tomographic scan showed a large tumor of the left kidney with probable lytic lesions of the right pelvis.

Metastatic carcinoma is the most common intraocular malignant neoplasm in adults and may be the first manifestation of systemic cancer. Metastases to the anterior segment occur much less frequently than to the choroid. Metastases to the iris have manifested as fleshy pink nodules, iris surface plaques, or iridocyclitis.[1] Renal cell carcinoma is a relatively rare cause of metastases to the iris, and has manifested as a gray- or yellow-white mass with prominent fine vascularization located on the inner portion of the iris surface.[1-4] The findings in our case are unusual because of the manifestation of a metastatic iris tumor as a smooth-domed, cystic-appearing mass, simulating an epithelial inclusion cyst, in a patient with aphakia. The coexistence of rubeosis and progressive glaucoma suggested the true nature of the lesion.

References

1. Ferry, A. P., and Font, R. L.: Carcinoma metastatic to the eye and orbit. II. A clinicopathological study of 26 patients with carcinoma metastatic to the anterior segment of the eye. Arch. Ophthalmol. 93:472, 1975.

2. Chance, B. K.: A case of secondary hypernephroma of the iris and ciliary body. Trans. Am. Ophthalmol. Soc. 11:178, 1906.

3. Hudson, A. C., and Lister, W.: Metastatic hypernephroma of the iris. Proc. R. Soc. Med. 27:1613, 1934.

4. Wyzinski, P., Rootman, J., and Wood, W.: Simultaneous bilateral iris metastases from renal cell carcinoma. Am. J. Ophthalmol. 92:206, 1981.

Meibomian Gland Carcinoma in a 20-year-old Patient

Jatinder S. Bhalla, M.S., S. Vashisht, M.S., Vijay K. Gupta, M.S., and A. K. Sen, M.D.

Departments of Ophthalmology (J.S.B., S.V., V.K.G.) and Pathology (A.K.S.), Deen Dayal Upadhyaya Hospital.

Inquiries to Jatinder S. Bhalla, M.S., D-1/4, Deen Dayal Upadhyaya Hospital Residential Complex, Hari Nagar, New Delhi 110064, India.

In January 1989, a 20-year-old woman had a rapidly growing swelling on her left upper eyelid for six months (Fig. 1). The patient had undergone incision and curettage of this swelling three months previously. She had not received radiotherapy. On examination, a small swelling of 5 × 3 mm was noted on the eyelid



Fig. 1 (Bhalla and associates). Growth on the left upper eyelid.

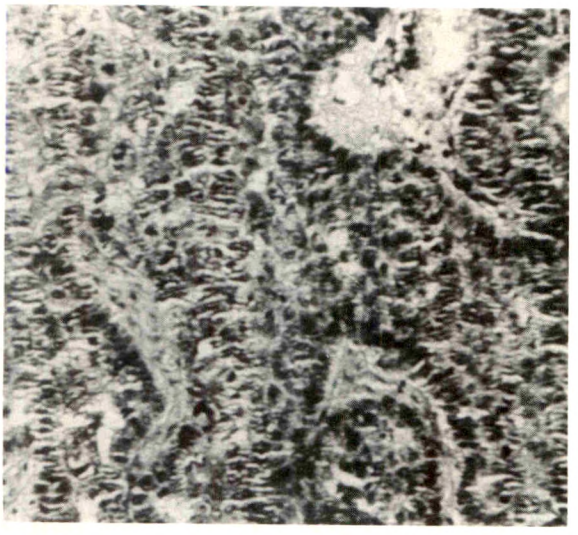


Fig. 2 (Bhalla and associates). Moderately differentiated meibomian cell carcinoma of the eyelid showing cells arranged in acinar formation around a central fibrovascular tissue (hematoxylin and eosin, ×440).

margin at the junction of the medial two thirds and lateral one third of the eyelid. The swelling originated from the tarsus. It was firm, nonmobile, and nontender. The upper eyelid also showed congestion.

Excision of the growth was performed. Meibomian gland carcinoma was diagnosed on histopathologic examination of the biopsy specimen (Fig. 2). The patient was again examined for any evidence of systemic involvement. Examination showed no lymphadenopathy or organomegaly. Results of x-rays of the orbit, chest, and long bones were normal.

In April 1990, the patient again had severe swelling on the left upper eyelid, measuring 10 × 13 mm. The swelling involved most of the eyelid, except for the medial 2 mm, and was found to be extending onto tarsal conjunctiva as a polypoid mass. The mass showed areas of ulceration and was friable and tender. Results of systemic examination were normal. A complete excision of the growth was performed and the upper eyelid was reconstructed.

On histopathologic examination, the tumor was found to be a moderately differentiated sebaceous adenocarcinoma. Oil-red-O stain for intracytoplasmic fat was present. The cells were mostly arranged in acinar formation around a central fibrovascular tissue. The cells showed vesicular nuclei containing basophilic material and prominent nucleoli.

Meibomian carcinoma is a rare but highly lethal tumor. Although it comprises only 0.2% to 1.3% of all eyelid tumors, it is the most malignant tumor of the eyelid, with mortality estimated from 6% to 30%.[1,2] The tumor characteristically develops late in life, and the average age of patients at diagnosis is 61 years.[2] In patients with meibomian carcinoma before the age of 40 years, the tumor usually has occurred after radiation therapy either for retinoblastoma[3] or cavernous hemangioma.[4] Our patient developed carcinoma at a young age without apparent exposure to any known carcinogen or radiation. In females, the tumor incidence is 1.5 to 2.75 times greater than in males.[5]

This lesion clinically resembles other less aggressive eyelid lesions. It is often mistaken for chalazion, which it may simulate or cause. The rate of growth is slow, often requiring one year to reach a noticeable size. The delay between onset of symptoms and diagnosis ranges from one to three years.

References

1. Cavanagh, H. D., Green, W. R., and Goldberg, H. K.: Multicentric sebaceous adenocarcinoma of meibomian gland. Am. J. Ophthalmol. 77:326, 1974.

2. Wagener, M. D., Beyer, C. K., Gonder, J. R., and Albert, D. M.: Common presentations of sebaceous gland carcinoma of the eyelid. Ann. Ophthalmol. 14:159, 1982.

3. Forest, A. W.: Tumors following radiation about eyes. Trans. Am. Acad. Ophthalmol. Otolaryngol. 65:694, 1961.

4. Schlernitzauer, D. A., and Font, R. L.: Sebaceous gland carcinoma of eyelid following radiation therapy for cavernous hemangioma of face. Arch. Ophthalmol. 94:1523, 1976.

5. Older, J. J.: Eyelid Tumors. Clinical Diagnosis and Surgical Treatment. New York, Raven Press, 1987, pp. 17–21.

A New Instrument for Use in Evisceration

William L. White, M.D., and Donald A. Hollsten, M.D.

Ophthalmology Service, Department of Surgery, Brooke Army Medical Center. The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the

views of the Department of the Army or the Department of Defense.

Inquiries to LTC. Donald A. Hollsten, M.D., M.C., U.S.A., Ophthalmology Service, Department of Surgery, Brooke Army Medical Center, Ft. Sam Houston, TX 78234-6200.

Archer and Hurwitz[1] stated that evisceration is preferable to enucleation to achieve better appearance, less orbital disruption, less enophthalmos, and better motility. Dermis-fat grafts used in conjunction with evisceration have also been proven to be a worthwhile procedure.[1] Although sympathetic ophthalmia after evisceration is rare, it has been reported.[2] Given the increase in frequency of this procedure in our institution and the desire to remove as much uveal tissue as possible, we have used an instrument smaller than the standard 12-mm (or 8-mm) Bunge evisceration spoons (Storz, Inc., St. Louis, Missouri).

The Rhoton spatulas (Codman and Shurtleff, Inc., Randolph, Massachusetts) are a collection of titanium instruments used in neurosurgical dissections. We have found two of them to be particularly useful in performing eviscerations. The sharp dissector, No. 5, is bent at a mild angle and allows for easy disinsertion of the anterior uveal elements (Figure). The round dissector, No. 3, is bent at a more acute angle with a 3.3-mm disk, which provides easier posterior manipulation and transsection of the optic nerve fibers. Since both instruments have a dull finish, they are especially well suited for use with the operating microscope, which we use routinely for all eviscerations.

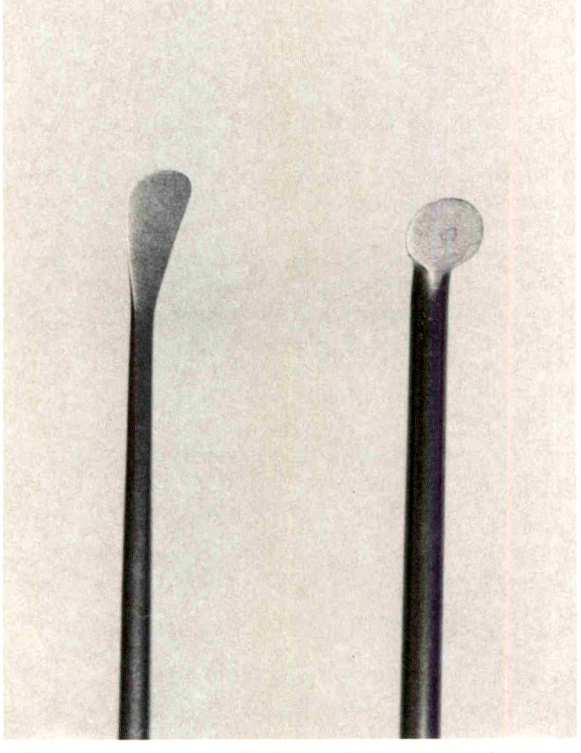


Figure (White and Hollsten). Rhoton round dissector, No. 3 (left) and sharp dissector, No. 5 (right).

References

1. Archer, K. F., and Hurwitz, J. J.: Dermis-fat grafts and evisceration. Ophthalmology 96:170, 1989.

2. Green, W. G., Maumenee, A. E., Sanders, T. E., and Smith, M. E.: Sympathetic uveitis following evisceration. Trans. Am. Acad. Ophthalmol. Otolaryngol. 76:625, 1972.

Flavobacterium meningosepticum Keratitis Successfully Treated With Topical Trimethoprim-Sulfamethoxazole

Frank A. Bucci, Jr., M.D., and Edward J. Holland, M.D.

Department of Ophthalmology, University of Minnesota School of Medicine.

Inquiries to Edward J. Holland, M.D., Department of Ophthalmology, UMHC Box 493, 516 Delaware St. S.E., Minneapolis, MN 55455.

Flavobacterium meningosepticum is a known cause of rare epidemics of fatal neonatal meningitis. Isolation of these bacteria from an ocular infection has been reported.[1] We treated a patient with *F. meningosepticum* keratitis successfully with topical trimethoprim-sulfamethoxazole. Treatment with topical trimethoprim-sulfamethoxazole has been reported in three cases of keratitis caused by *Nocardia asteroides*.[2-4]

An 82-year-old woman with a history of glaucoma secondary to a central retinal vein occlusion and subsequent enucleation of the right eye had a red, painful left eye. A central trophic

corneal ulcer secondary to trichiasis, dry eye, a poor blink reflex, and exposure was diagnosed. Despite medical therapy, the condition progressed to a central corneal perforation six months later. Cyanoacrylate gluing was unsuccessful. An 8.2-mm lamellar corneal graft was sutured into a 7.7-mm recipient bed. A punctate epithelial keratopathy of the lamellar graft developed into a persistent epithelial defect. This defect healed after a large lateral tarsorrhaphy was performed.

Nine months after the lamellar graft, the patient had a large nasal epithelial defect. The lateral tarsorrhaphy was intact. After maximum lubrication and taping the eyelid closed at night, but the persistent epithelial defect did not resolve. When a corneal infiltrate and discharge developed, infectious keratitis was suspected. Cultures were obtained from corneal scrapings, and the patient was given fortified vancomycin hydrochloride (33 mg/ml) and tobramycin (15 mg/ml) eyedrops every hour. The initial Gram stain showed no organisms. A single colony was observed at 48 hours. A Gram stain of this colony at 72 hours disclosed a gram-negative rod. At 96 hours, the organism was identified as *F. meningosepticum*. This organism was resistant to all antibiotics tested, except trimethoprim-sulfamethoxazole, and was intermediately sensitive to gentamicin sulfate. The organism was resistant to amikacin, tobramycin, chloramphenicol, piperacillin sodium, ticarcillin, ampicillin, tetracycline, and various cephalosporin derivatives.

No improvement was observed during the four-day period before identifying the organism (Figure). Sulfacetamide 30% and fortified gentamicin sulfate (15 mg/ml) eyedrops given every hour for five days yielded no improvement. Trimethoprim (16 mg/ml) and sulfamethoxazole (80 mg/ml) eyedrops prepared directly from the commercial intravenous solution were administered every 30 minutes while the patient was awake and every hour while asleep. Significant clinical improvement was observed within three days, and the trimethoprim-sulfamethoxazole eyedrops were decreased to every two hours while awake and every four hours while asleep. The corneal infiltrate and epithelial defect gradually resolved over a period of 12 days. The patient was discharged on a regimen of trimethoprim-sulfamethoxazole four times a day, which was tapered over a two-week period.

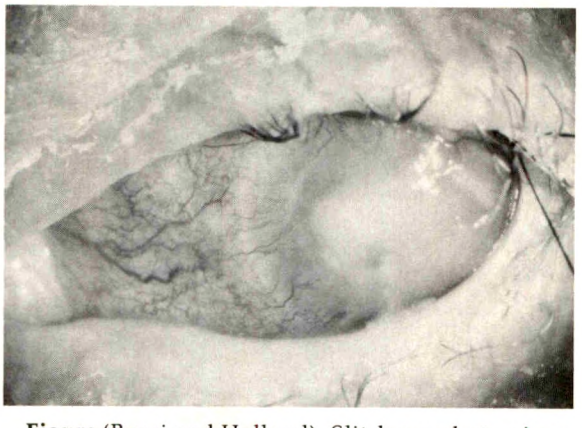


Figure (Bucci and Holland). Slit-lamp photomicrograph of the corneal ulcer at the time *F. meningosepticum* was identified.

Flavobacterium meningosepticum is a nonfermenting, aerobic, gram-negative bacillus in the same genera as *Pseudomonas* species and is most widely known as a cause of neonatal meningitis. It is not a part of the normal ocular flora. It produces a yellow pigment that helps distinguish it from nonpigmented strains of *P. aeruginosa*. As observed in our patient, *F. meningosepticum* is characterized by a limited spectrum of antimicrobial sensitivity. It is usually resistant to most antibiotics tested, including the aminoglycosides. It has been reported to be sensitive to rifampin, erythromycin, and trimethoprim-sulfamethoxazole. Isolation of an atypical *Pseudomonas* species with an unusual antibiotic sensitivity pattern, as observed in another ocular infection reported from this organism,[1] should alert the clinician to consider *F. meningosepticum* in the differential diagnosis.

The pathogenicity of *P. aeruginosa* is derived from the production of an elastase with proteolytic activity. *Flavobacterium meningosepticum* also produces an elastase structurally similar to that produced by *Pseudomonas* species. Animal experiments have demonstrated a lower virulence of the elastase isolated from strains of *F. meningosepticum*.[5] Proteolytic activity has been absent in selected samples of elastase isolated from various strains of this organism. Additionally, the production of a keratitis in rabbits required many more whole viable cells of *F. meningosepticum* when compared with *P. aeruginosa*.[5] This helps explain the rare occurrence of ocular infections caused by these bacteria, although the actual incidence may be somewhat greater than the number of reported cases would indicate. The compromised ocular sur-

face of our patient probably explains why the eye was infected by an organism demonstrating such a relatively low level of virulence.

References

1. LeFrançois, M., and Baum, J. L.: *Flavobacterium* endophthalmitis following keratoplasty. Arch. Ophthalmol. 94:1907, 1976.
2. Donnenfeld, E. D., Cohen, E. J., Barza, M., and Baum, J.: Treatment of *Nocardia* keratitis with topical trimethoprim-sulfamethoxazole. Am. J. Ophthalmol. 99:601, 1985.
3. Perry, H. D., Nauheim, J. S., and Donnenfeld, E. D.: *Nocardia asteroides* keratitis presenting as a persistent epithelial defect. Cornea 8:41, 1989.
4. Enyenauer, R. W., Cornell, F. M., Brooke, J. D., and Butler, C. E.: *Nocardia asteroides* keratitis. A case associated with soft contact lens wear. CLAO J. 15:71, 1989.
5. Miyazaki, S.: Biological activities of partially purified elastase produced by *Flavobacterium meningosepticum*. Microbiol. Immunol. 28:1083, 1984.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Pneumocystis carinii Choroiditis After Long-term Aerosolized Pentamidine Therapy

EDITOR:

We read with interest the article "*Pneumocystis carinii* choroiditis after long-term aerosolized pentamidine therapy," by P. U. Dugel, N. A. Rao, D. J. Forster, L. P. Chong, G. T. Frangieh, and F. Sattler (Am. J. Ophthalmol. 110:113, August 1990). We agree that an early ophthalmic examination may detect extrapulmonary *P. carinii* infections before there are any clinical signs of disseminated disease elsewhere in patients with acquired immunodeficiency syndrome receiving prophylactic treatment with aerosolized pentamidine. We believe, however, that two points deserve emphasis. Firstly, some of these patients may have no visual complaints as well as normal visual acuity despite extensive choroidal lesions involving the macula.[1] Thus, routine ophthalmic screening is certainly desirable. Secondly, as the authors point out, it is likely that both of their patients may have had occult dissemination of *P. carinii* to other organs. Unfortunately, there is no mention in their article of the performance of gallium scans. This procedure is useful in detecting *P. carinii* lesions in the lungs and elsewhere.[2] For instance, we recently examined a patient with AIDS and *P. carinii* choroiditis who used aerosol pentamidine prophylaxis. The only other evidence of extrapulmonary dissemination was the presence of increased uptake of gallium in the thyroid gland. This would not have been detected with abdominal computed tomography or any of the other tests performed by the authors. Involvement of the thyroid gland with *P. carinii* has been previously reported.[3]

We wish to emphasize the importance of ophthalmic screening even in visually asymptomatic patients with AIDS who receive aerosolized pentamidine prophylaxis and the use of a gallium scan in the systemic examination of those patients in whom choroidal lesions are detected.

STEVEN A. TEICH, M.D.
MARC ROSENBLATT, M.D.
ALAN FRIEDMAN, M.D.
New York, New York

References

1. Rosenblatt, M. A., Teich, S. A., Friedman, A. H., and Cunningham, C.: Choroidal lesions in patients with AIDS. Br. J. Ophthalmol. In press.
2. Woolfenden, J. M., Carrasquillo, J. A., Larson, S. M., Simmons, J. T., Masur, H., Smith, P. D., Shelhamer, J. H., and Ognibene, F. P.: Acquired immunodeficiency syndrome. GA-67 citrate imaging. Radiology 162:383, 1987.
3. Gallant, J. E., Enriquez, R. E., Cohen, K. L., and Hammers, L. W.: *Pneumocystis carinii* thyroiditis. Am. J. Med. 84:303, 1988.

Reply

EDITOR:

Drs. Teich, Rosenblatt, and Friedman are correct in emphasizing that asymptomatic mul-

tifocal choroiditis may be the first and only manifestation of disseminated *Pneumocystis carinii* infection. We believe, however, that routine gallium scan screening of such patients may not be useful. We have used gallium scans and found them to be sensitive but nonspecific. This has been corroborated in published reports. Despite a sensitivity near 100%, the specificity in patients with AIDS and *P. carinii* pneumonia may be as low as 20%.[1] Although isolated reports have claimed a specificity of as high as 95%,[2] pooled data on gallium scanning for *P. carinii* pneumonia in patients with AIDS show a sensitivity of 98% and a specificity of only 47%.[3] Until the predictive value of gallium scanning for occult extrapulmonary infections is better studied, we conclude, based upon our experience and the studies of *P. carinii* pneumonia, that routine gallium scan screening cannot be recommended.

The significance of isolated increased thyroidal uptake of gallium, even in a patient with multifocal choroiditis, is unclear. The clinical thyroid examination of the patient mentioned by Drs. Teich, Rosenblatt, and Friedman was not described. The patient described by Gallant and associates[4] demonstrated rapid enlargement of the thyroid gland. We recently examined four patients with AIDS with similar thyroid gland enlargement that was proved to be caused by *P. carinii* by fine needle aspiration. Therefore, without clinical findings, the meaning of a positive gallium scan is unclear.

Rao and associates[5] have shown that patients with *P. carinii* choroiditis inevitably have dissemination to many organ systems. We believe that all patients with previous *P. carinii* pneumonia while taking aerosolized pentamidine and multifocal choroiditis should be treated with intravenous pentamidine (4 mg/kg of body weight per day) or trimethoprim (20 mg/kg of body weight per day) and sulfamethoxazole (100 mg/kg of body weight per day) for three weeks, regardless of any imaging studies. Such prompt diagnosis and treatment may indeed preserve sight and life.

PRAVIN U. DUGEL, M.D.
NARSING A. RAO, M.D.
DAVID J. FORSTER, M.D.
LAWRENCE P. CHONG, M.D.
GEORGE T. FRANGIEH, M.D.
FRED SATTLER, M.D.
JOHN A. LOPRESTI, M.D.
Los Angeles, California

References

1. Coleman, D. L., Hattner, R. S., Luce, J. M., Doder, P. M., Golden, J. A., and Murray, J. F.: Correlation between gallium lung scans and fiber optic bronchoscopy in patients with suspected *Pneumocystis carinii* pneumonia and the acquired immune deficiency syndrome. Am. Rev. Respir. Dis. 130:1166, 1984.

2. Woolfenden, J. M., Carrasquillo, J. A., Larson, S. M., Simmons, J. T., Masur, H., Smith, P. D., Shelhamer, J. H., and Oguibene, F. P.: Acquired immunodeficiency syndrome. GA-67 citrate imaging. Radiology 162:383, 1987.

3. Murray, J. F., Felton, C. P., Garay, S. M., Gottlieb, M. S., Hopewell, P. C., Stover, D. E., and Teirstein, A. S.: Pulmonary complications of the acquired immunodeficiency syndrome. N. Engl. J. Med. 310:1682, 1984.

4. Gallant, J. E., Enriquez, R. E., Cohen, K. L., and Hammers, L. W.: *Pneumocystis carinii* thyroiditis. Am. J. Med. 84:303, 1988.

5. Rao, N. A., Zimmerman, P. L., Boyer, D., Biswas, J., Causey, D., Beniz, J., and Nichols, P. W.: A clinical, histopathologic, and electron microscopic study of *Pneumocystis carinii* choroiditis. Am. J. Ophthalmol. 107:218, 1989.

The Gradient Filter Test to Assess Amblyopia

EDITOR:

In the article "The gradient filter test to assess amblyopia," by R. V. Keech and P. J. Kutschke (Am. J. Ophthalmol. 110:57, July 1990), a set of calibrated fog filter and prism lenses was proposed to assess visual acuity indirectly in amblyopic eyes. The fog prism lens is placed in front of the normal fixing eye and the greatest density filter, which causes a switch in fixation, is noted as an indirect measurement of visual acuity. This test is a variant of the test proposed by Cadera and associates[1] and is subject to the same criticism.[2] These two tests, like the red filter bar test of Bagolini,[3] measure suppression. Suppression is a binocular phenomenon, and there is no theoretical or practical basis for correlating it with monocularly determined visual acuity.

I described two patients who maintained fixation with the dominant eye after successful amblyopia treatment, even though visual acuity in the dominant eye was reduced compared

to that of the amblyopic eye.[4] The findings in these patients showed that the pattern of fixation is not an index of monocular visual acuity. Suppression is produced by an active inhibition from the afferences of the fixing eye. Altering the sharpness of the image perceived by the fixing eye results in an indirect measurement of this inhibitory process and not in an indirect measurement of visual acuity of the amblyopic eye. Suppression and visual acuity are two different measurements, even if both generally improve after occlusion therapy. This correlation, however, is not absolute. Two patients described by Dr. Keech and Ms. Kutschke showed an improvement in visual acuity not detected by the gradient filter test. For these reasons, the gradient filter test, unlike forced choice preferential looking methods, cannot be considered as a test for visual acuity measurements.

I agree that, in the preverbal child with strabismus, the assessment of fixation is a useful method for monitoring amblyopia treatment. I agree also that the gradient filter test may be useful in detecting a reduction of suppression. In my opinion, however, to speak of this test in terms of visual acuity is incorrect.

MARCO NARDI, M.D.
Cagliari, Italy

References

1. Cadera, W., Pachtman, M. A., Ellis, F. D., and Helveston, E. M.: Depth of strabismic amblyopia determined with neutral density filters. Am. J. Ophthalmol. 95:763, 1983.

2. Nardi, M.: Depth of strabismic amblyopia determined with neutral density filters. Am. J. Ophthalmol. 97:400, 1984.

3. Bagolini, B.: Presentazione di una sbarra filtri a densità scalare assorbenti i raggi luminosi. Boll. Ocul. 36:638, 1957.

4. Nardi, M.: Persistence of suppression after treatment for strabismic amblyopia. Some remarks on two particular cases. J. Fr. Ophtalmol. 4:833, 1981.

Reply

EDITOR:

We appreciate Dr. Nardi's comments regarding the differences between subjective visual acuity tests and pattern preference methods, such as the gradient filter test. Despite his contention that the gradient filter test measures suppression and has no basis for correlating with visual acuity, we believe there is considerable evidence to support the value of this test in detecting a change in visual acuity between the amblyopic and nonamblyopic eye of a patient. As Dr. Nardi agrees, the use of fixation pattern methods as a means for evaluating amblyopia treatment is well established.[1] This is thought to be because the fixation response correlates with the visual acuity difference between the normal and amblyopic eyes of patients.

We are aware that fixation pattern methods do not correlate well with visual acuity measurements in older individuals, such as in the patients Dr. Nardi described, or in patients with little or no ocular misalignment. The gradient filter test and other fixation preference tests, however, are intended to be used in preverbal children in whom there is a good correlation between fixation response and visual acuity.[2] In patients with little or no ocular misalignment, the visual acuity difference between the amblyopic and nonamblyopic eyes can be assessed accurately when the fixation pattern is tested with a 10-diopter base-down prism placed over one eye. This technique is thought to be more accurate than a standard fixation preference test because the prism places the object of regard in the amblyopic eye outside the suppression scotoma when the patient is fixing with the normal eye.[3] For this reason, the gradient filter test incorporates a 12-diopter base-down prism with the calibrated fog filters.

Dr. Nardi notes that subjective visual acuity improved during a single patching episode in two patients in our study without an equivalent improvement documented with the gradient filter test. He cites this as evidence that the gradient filter test measures suppression and not visual acuity. It should be emphasized that both of these patients had minimal improvement in subjective visual acuity during the specified patching episodes. Visual acuity improved in one patient from 20/60 to 20/50 with linear illiterate E test and in the other patient from 20/60 to 20/50 with Allen pictures. In the ten other patching episodes documented in the study, the optotype tests and the gradient filter test both detected an improvement in visual acuity. It should be apparent, therefore, that the gradient filter test can identify accurately a change in visual acuity between the amblyopic and nonamblyopic eyes

of children undergoing occlusion treatment for amblyopia by quantitating a change in fixation preference.

RONALD V. KEECH, M.D.
PAMELA J. KUTSCHKE, B.S.
Iowa City, Iowa

References

1. Zipf, R. F.: Binocular fixation pattern. Arch. Ophthalmol. 94:401, 1976.
2. Campos, E. C., and Gulli, R.: Lack of alternation in patients treated for strabismic amblyopia. Am. J. Ophthalmol. 99:63, 1985.
3. Wright, K. W., Edelman, P. M., Walonker, F., and Yiu, S.: Reliability of fixation preference testing in diagnosing amblyopia. Arch. Ophthalmol. 104:549, 1986.

Vitrectomy Retinotomy Aspiration Biopsy of Choroidal Tumors

EDITOR:

In the article "Vitrectomy retinotomy aspiration biopsy of choroidal tumors," by D. M. Fastenberg, P. T. Finger, Q. Chess, J. H. Koizumi, and S. Packer (Am. J. Ophthalmol. 110:361, October 1990), the authors describe a new biopsy technique for choroidal tumors involving vitrectomy, retinotomy, and tumor biopsy.

Apparently the use of vitrectomy instrumentation should differentiate their technique from others. With brief literature search they would have found that vitrectomy has been an indispensable part of the method of internal resection I have described in animals and humans.[1-3] I wonder, however, if it is prudent to go to the trouble of performing a vitrectomy and retinotomy and leave the remaining tumor inside the eye when it is possible to remove it completely.

GHOLAM A. PEYMAN, M.D.
New Orleans, Louisiana

References

1. Peyman, G. A., and Barrada, A.: Retinochoroidectomy ab interno. Ophthalmic Surg. 15:749, 1984.
2. Peyman, G. A., and Cohen, S. B.: Ab interno resection of uveal melanoma. Int. Ophthalmol. 9:29, 1986.
3. Peyman, G. A., and Gremillion, C. M., Jr.: Eye wall resection in the management of uveal neoplasms. Jpn. J. Ophthalmol. 33:458, 1989.

Reply

EDITOR:

We acknowledged Dr. Peyman's work on the use of vitrectomy instrumentation in the management of uveal melanomas.[1] The purpose of our article was to offer an alternative biopsy technique to that of a fine needle aspiration biopsy.[2] We believe that vitrectomy retinotomy aspiration biopsy may have advantages over that technique in terms of offering more control, minimizing complications, and possibly delivering more tumor for cytopathologic testing.

In response to the question as to whether it is prudent to leave remaining tumor tissue in the eye after biopsy, we must note that in those eyes found to have choroidal melanomas, treatment either by plaque therapy or enucleation was recommended. We emphasize that our procedure is offered only as a biopsy technique.

DAVID M. FASTENBERG, M.D.
PAUL T. FINGER, M.D.
QUINTUS CHESS, M.D.
SAMUEL PACKER, M.D.
Manhasset, New York
JUNE H. KOIZUMI, M.D.
New York, New York

References

1. Peyman, G. A., and Cohen, S. B.: Ab interno resection of uveal melanoma. Int. Ophthalmol. 9:29, 1986.
2. Augsburger, J. J., and Shields, J. A.: Fine needle aspiration biopsy of solid intraocular tumors. Indications, instrumentation, and techniques. Ophthalmic Surg. 15:34, 1984.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Thyroid Eye Disease, ed. 2. By Devron H. Char. New York, Churchill Livingstone Inc., 1990. 229 pages, index, illustrated. $59.95

Reviewed by JOEL WEINSTEIN
Madison, Wisconsin

The diagnosis and treatment of thyroid ophthalmopathy has been a troublesome area since this disorder was first recognized almost 200 years ago. In the first edition of this book, published in 1985, the author's stated purpose was to "consolidate current ideas of pathogenesis, diagnosis, and management." The first edition succeeded admirably in synthesizing this complex area and in providing the practitioner with a rational basis for diagnostic and therapeutic decisions. The second edition has changed little from the first.

The early chapters elucidate the normal regulatory mechanisms for thyroid hormone synthesis and describe the biochemical and immunologic tests used in the diagnosis of thyroid disease. The author provides a useful protocol for detection of thyroid abnormalities in those patients whose orbital signs are not diagnostic of Graves' disease. Later chapters discuss the natural progression of Graves' disease and the details of various therapeutic modalities including corticosteroids, immunosuppressives, radiation, and surgery. Although not all specialists would agree with all of the author's therapeutic recommendations (for example, the use of radiation therapy for soft tissue inflammation without visual loss), each chapter is thoroughly referenced, and the reader who senses a controversial or difficult area has all of the current and historic references provided for personal decision making.

This book is the best comprehensive review of this difficult and complex subject. It will be a valuable addition to the library of any practicing ophthalmologist.

Normal Pressure Glaucomas. By Alain Bechetoille. France, Service Ophtalmologie, 1990. 259 pages, index, illustrated. $52

Reviewed by PIERRE BLONDEAU
Sherbrooke, Canada

This is a collection of the papers and posters presented at an international symposium on normal pressure glaucoma held in Angers, France, in June 1989. The symposium was held to honor Dr. Stephen Drance's contribution to this area of glaucoma research. Representatives of nine different countries, with the largest representation being from France, attended this meeting.

The text is subdivided into a paper section and a poster section. It begins with a biography of Albrecht von Graefe, who first described normal pressure glaucoma. Dr. Drance then summarizes current views on the topic.

Topics include optic nerve development and anatomy, biomorphometry of the optic disk by image analysis, and nerve fiber layer photography. The contributions made to glaucomatous optic neuropathy by the blood supply of the optic nerve head, axonal transport disturbances, and mechanical factors are described.

An unusual feature of this book is that all the papers are printed side-by-side in both French and English. The text of the original language is in one typeface, but the translation is always in another. If one reads only in English, the typeface keeps changing, and this is disconcerting until the logic is understood. The translations are, for the most part, excellent. There are rare mistakes that change the meaning of the sentence and occasionally a sentence is entirely missing. The tables and figures remain in the original language, but the legends to the figures are published in French and English.

This short text presents our current understanding of normal pressure glaucoma and outlines future areas of research. It will be a valuable source of information to any ophthalmologist or resident interested in this common condition that challenges our understanding of glaucoma. When we understand normal pressure glaucoma we will be well on our way to understanding the process of glaucomatous optic nerve damage.

Books Received

Vom Helmholtz-Augenspiegel zur Funduskamera. By Alfred Schett. Switzerland, Verlag Sauerlander, 1990. 82 pages, index, illustrated. (No price given)

This monograph is a catalog of the collection of old ophthalmoscopes and related instru-

ments in the Museum of the History of Medicine of the University of Zurich. There are photographs of each item, beginning with Helmholtz's first instrument in 1851. By 1870, most ophthalmoscopes contained a rotary rack of lenses and were becoming increasingly compact and portable.

In the 1920s and 1930s electric ophthalmoscopes became available, with considerable loss in portability. Table-top instruments with improved optics appeared, which were the precursors of the fundus camera.

This book, which is carefully and thoroughly annotated by Alfred Schett, will be prized by instrument collectors and historians.

Year Book of Ophthalmology 1990. Edited by Peter R. Laibson. St. Louis, Mosby–Year Book, 1990. 262 pages, index, illustrated. $54.95

A fascinating guided tour through the ophthalmic literature of 1989–1990 led by the Wills Eye Hospital faculty.

The Book List

Atlas of Ophthalmic Surgery. By Norman S. Jaffe. Philadelphia, J. B. Lippincott, 1989. 320 pages, index, illustrated. $175

Cataract Surgery. Alternative Small-Incision Techniques. Edited by George W. Rozakis. Thorofare, Slack, Inc., 1990. 194 pages, index, illustrated. $95 (videotape included)

Clinical Tests of Vision. By Lars Frisen. New York, Raven Press, 1990. Softcover, 212 pages, index, illustrated. $59

Handbook of Ocular Drug Therapy and Ocular Side Effects of Systemic Drugs. By Deborah Pavan-Langston and Edmund C. Dunkel. Boston, Little, Brown and Company, 1990. Softcover, 464 pages, index, illustrated. $32.50

Lens Implant Power Calculation, ed. 3. By John A. Retzlaff, Donald R. Sanders, and Manus Kraff. Thorofare, Slack, Inc., 1990. Softcover, 58 pages, illustrated. $20

Manual of Visual Fields. By Elliot B. Werner. New York, Churchill Livingstone, Inc., 1990. Softcover, 238 pages, index, illustrated. $39

Ophthalmology Clinics of North America. By Everett Ai and William R. Freeman. Philadelphia, W. B. Saunders, 1990. 536 pages, index, illustrated. $31

Practical Management of Squint. By Graham Pittar. Wahroonga, Australia, Turton & Armstrong Pty. Ltd., 1990. 341 pages, index, illustrated. $147

Retinal Nerve Fiber Layer Photography. By Louis W. Roloff. Thorofare, Slack, Inc., 1990. 174 pages, illustrated. $90

Visual Allusions. Pictures of Perception. By Nicholas Wade. East Sussex, England, Lawrence Erlbaum Associates, Ltd., 1990. 288 pages, index, illustrated. $42.95

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

Cloning of a gene that is rearranged in patients with choroideraemia. Cremers, F. P. M.*, van de Pol, D. J. R., van Kerkhoff, L. P. M., Wieringa, B., and Ropers, H.-H.: Nature 347:674, 1990.

CHOROIDEREMIA, GENETICS

Choroideremia, a common form of X-linked blindness, is characterized by progressive dystrophy of the choroid, retinal pigment epithelium, and retina. Using reverse genetic strategies, the authors isolated eight overlapping complementary DNA clones from the same chromosomal region. The corresponding gene was expressed in retina, choroid, and retinal pigment epithelium. The cDNAs encompassed an open reading frame of 948 base pairs that was structurally altered in eight patients with choroideremia with deletions, and in a woman with a balanced translocation involving the Xq21 region of the X chromosome. These findings provide strong evidence that the authors have cloned the gene underlying choroideremia. Elucidation of its function should provide new insights into the molecular mechanisms responsible for this disorder.—Michael A. Kass

*Department of Human Genetics, University Hospital, University of Nijmegen, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Retinal degeneration in the rd mouse is caused by a defect in the β subunit of rod cGMP-phosphodiesterase. Bowes, C., Li, T., Danciger, M., Baxter, L. C., Applebury, M. L., and Farber, D. B.*: Nature 347:677, 1990.

RETINAL DEGENERATION, RETINITIS PIGMENTOSA, GENETICS

Mice homozygous for the rd mutation develop a retinal degeneration that is a model for human retinitis pigmentosa. In affected animals, the retinal rod photoreceptors begin degenerating at approximately postnatal Day 8, and by four weeks no photoreceptors remain. Degeneration is caused by deficient activity of the rod photoreceptor cGMP-phosphodiesterase, which causes an accumulation of cyclic GMP in the retina. The authors isolated a candidate complementary DNA for the rd gene from a mouse retinal library and completed the characterization of cDNAs encoding all subunits of bovine photoreceptor phosphodiesterase. The candidate cDNA showed strong homology with a cDNA encoding the bovine phosphodiesterase β subunit. It seems likely that the normal counterpart of the rd gene encodes the rod photoreceptor cGMP-phosphodiesterase β subunit.—Michael A. Kass

*Jules Stein Eye Institute, University of California, Los Angeles, School of Medicine, Los Angeles, CA 90024.

Displacement of bag-placed hydrogel lenses into the vitreous following neodymium:YAG laser capsulotomy. Levy, J. H.*, Pisacano, A. M., and Anello, R. D.: J. Cataract Refract. Surg. 16:563, 1990.

HYDROGEL INTRAOCULAR LENS, YAG CAPSULOTOMY, DISLOCATED IMPLANT

In two patients hydrogel intraocular lens implants dislocated posteriorly into the vitreous after YAG laser capsulotomy. Both patients had had cataract surgery, including capsulorhexis, and insertion of a hydrogel lens by a syringe technique. Both patients underwent YAG capsulotomy seven weeks after cataract surgery. No movement of the implants was observed at the time of the operation. Two weeks after laser treatment, however, the patients had decreased visual acuity, and the implants were in the vitreous. The dislocated hydrogel lenses were removed, and the patients received polymethylmethacrylate implants in the sulcus. It is not clear whether this represents a chance occurrence or if there is some underlying problem with this type of implant.—Michael A. Kass

*New York Eye Surgery Center, 1101 Pelham Pkwy. N., Bronx, NY 10469.

Visual results and complications of transsclerally sutured intraocular lenses in pene-

trating keratoplasty. Heidemann, D. G.*, and Dunn, S. P.: Ophthalmic Surg. 21:609, 1990.

SUTURED POSTERIOR CHAMBER IMPLANTS, PENETRATING KERATOPLASTY

Fifty-six consecutive patients underwent penetrating keratoplasty with transscleral fixation of posterior chamber implants. The follow-up ranged from three to 28 months (mean, 11.1 months). Postoperative visual acuity improved in 46 patients (82%), remained the same in eight (14%), and worsened in two (3.6%). In 32 patients with at least ten months of follow-up, visual acuity as measured with a pinhole or hard contact lens was 20/40 or better in 12 (38%), 20/50 to 20/100 in ten (31%), and 20/200 or worse in ten (31%). There were minimal problems with lens decentration, tilt, or infections related to the scleral sutures. Glaucoma was the most common cause of decreased vision in patients with ten or more months of follow-up. Three patients (5.4%) developed rhegmatogenous retinal detachments early in the postoperative course. A prospective randomized trial will be necessary to compare the results of penetrating keratoplasty with implantation of anterior chamber intraocular lenses to penetrating keratoplasty with implantation of transsclerally sutured posterior chamber lenses.—Michael A. Kass

*Michigan Cornea Consultants, Southfield, MI 48013.

The human lens after 48 weeks of treatment with lovastatin. Laties, A. M., Keates, E. U., Taylor, H. R., Chremos, A. N., Shear, C. L., Lippa, E. A., Gould, A. L., and Hurley, D. P.: N. Engl. J. Med. 323:683, 1990.

CHOLESTEROL, LOVASTATIN, LENS OPACITIES

There has been some concern about whether lovastatin causes lens opacities. The authors summarize the ophthalmic findings of 8,245 patients who were on a cholesterol-lowering diet and who participated in a 362-center, randomly assigned, double-masked, placebo-controlled study lasting 48 weeks. Five groups of patients, each consisting of approximately 1,650 patients, received placebo, 20 mg of lovastatin once daily, 20 mg twice daily, 40 mg once daily, or 40 mg twice daily. At baseline and after 24 and 48 weeks, the lens of each eye was assessed by slit-lamp examination after dilation of the pupil. From 79% to 82% of the patients in each group completed the study and provided data for analysis. Analysis of the distribution of cortical, nuclear, and subcapsular opacities at 48 weeks showed no significant differences between the placebo and lovastatin groups. The placebo and lovastatin groups also did not differ in the incidence of visual acuity reduction of two lines or more. Thus, as of 48 weeks, there was no obvious effect of lovastatin on the human lens.—Michael A. Kass

Subconjunctival THC:YAG laser limbal sclerostomy ab externo in the rabbit. Hoskins, H. D., Jr.*, Iwach, A. G., Drake, M. V., Schuster, B. L., Vassiliadis, A., Crawford, J. B., and Hennings, D. R.: Ophthalmic Surg. 21:589, 1990.

LASER FILTERING SURGERY

A chromium-sensitized, and thulium and holmium-doped YAG laser (THC:YAG laser) was used to create bilateral limbal sclerostomies in six Dutch pigmented rabbits. The laser is a long-pulsed (300 ms), compact, self-contained, solid-state laser operating in the near infrared (2.1 μm). A 1-mm conjunctival stab incision was made 12 mm away from the sclerostomy site to allow entry of a specially designed 26-gauge (480 μm) optic probe that delivers energy at right angles to the long axis of the fiber. Probe insertion minimally disturbed the conjunctiva. Pulse energies of 60 to 150 mJ were used with a repetition rate of 5 pulses/s. Energy levels ranging from 1.35 to 6.6 J produced full-thickness sclerostomies. Histopathology showed a sharply defined perforating limbal wound at all energy levels. The overlying conjunctiva was intact, with swelling of the adjacent cornea. A peripheral iridectomy was intentionally created with the laser through the peripheral limbus, resulting in a sharply defined perforating tract through the iris/ciliary body. This technique may simplify filtering sclerostomy surgery, without anterior chamber instrumentation and with minimal conjunctival trauma.—Authors' abstract

*Foundation for Glaucoma Research, 490 Post St., Ste. 830, San Francisco, CA 94102.

Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Bergman, H.*, Wichmann, T., and DeLong, M. R.: Science 249:1436, 1990.

PARKINSON'S DISEASE, SUBTHALAMIC NUCLEUS

Although it is known that Parkinson's disease results from a loss of dopaminergic neurons in the substantia nigra, the resulting alterations in activity in the basal ganglia responsible for parkinsonian motor deficits are still poorly characterized. Recently, increased activity in the subthalamic nucleus has been implicated in the motor abnormalities. To test this hypothesis, the effects of lesions of the subthalamic nucleus were evaluated in monkeys rendered parkinsonian by treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). The lesions reduced all of the major motor disturbances in the contralateral limbs, including akinesia, rigidity, and tremor. This result supports the postulated role of excessive activity in the subthalamic nucleus in Parkinson's disease.—Authors' abstract

*Department of Neurology, Johns Hopkins Hospital, Baltimore, MD 21205.

Saccadic eye movements in essential blepharospasm. Lueck, C. J., Tanyeri, S., Crawford, T. J., Elston, J. S., and Kennard, C.*: J. Neurol. 237:226, 1990.

ESSENTIAL BLEPHAROSPASM, OCULAR MOVEMENTS, BASAL GANGLIA DISORDER

To provide evidence of an organic pathology for essential (idiopathic) blepharospasm, reflex saccadic eye movements in response to randomly stepped visual targets were assessed in seven affected patients and seven age-matched controls using the magnetic scleral search coil technique. The results indicate a significant prolongation in latency and a reduction in gain of horizontal saccades, and an increase in latency and reduction of peak velocity of large downward saccades. These findings suggest an organic component to the aetiology of blepharospasm, the pathology of which also appears to involve the oculomotor system. The pattern of the oculomotor disorder does not allow specific localisation but is consistent with the underlying pathology being localised in the basal ganglia.—Authors' abstract

*Department of Neurology, London Hospital, Whitechapel, London E1 1BB, United Kingdom.

A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes. Riley, W. J.*, Maclaren, N. K., Krischer, J., Spillar, R. P., Silverstein, J. H., Schatz, D. A., Schwartz, S., Malone, J., Shah, S., Vadheim, C., and Rotter, J. I.: N. Engl. J. Med. 323:1167, 1990.

CYTOPLASMIC ISLET-CELL AUTOANTIBODIES, INSULIN-DEPENDENT DIABETES MELLITUS, RISK FACTOR

It is now well established that insulin-dependent diabetes mellitus is an autoimmune disorder. The presence of cytoplasmic islet-cell autoantibodies has been recognized as a risk factor for the development of diabetes in relatives of patients with insulin-dependent diabetes. The authors studied 4,015 initially nondiabetic relatives of patients with insulin-dependent diabetes to determine whether the presence of the cytoplasmic islet-cell autoantibodies was a risk factor and how this interrelated with other risk factors. Of the 4,015 nondiabetic relatives, 125 (3.1%) had islet-cell antibodies in their initial serum samples. Of these individuals 40 eventually developed insulin-dependent diabetes. Islet-cell antibodies were most common in relatives who were younger than 20 years of age and in those from families with more than one affected member. Of these 40 patients, 27 (67.5%) of the relatives in whom diabetes developed had positive tests for islet-cell antibodies before the diagnosis of insulin-dependent diabetes, which gave a relative risk of 68 (95% confidence interval, 34 to 134). Thus, it appears that nondiabetic relatives of individuals with insulin-dependent diabetes mellitus who are in the first two decades of life, are members of families in whom there is more than one affected individual, and have increased titers of islet-cell autoantibodies are at high risk for developing insulin-dependent diabetes mellitus.—Michael A. Kass

*Department of Pathology, Box J-275, JHMHC, University of Florida College of Medicine, Gainesville, FL 32610.

Ending smoking at The Johns Hopkins Medical Institutions. An evaluation of smoking prevalence and indoor air pollution. Stillman, F. A.*, Becker, D. M., Swank, R. T., Hantula, D., Moses, H., Glantz, S., and Waranch, H. R.: JAMA 264:1565, 1990.

NICOTINE VAPOR CONCENTRATION, INSTITUTIONAL SMOKING POLICY

An empiric evaluation of a policy ending smoking in a large urban medical center was conducted. The study included a prospective cohort tracking of employees to measure changes in smoking behavior, environmental fires, smoking-related litter, and environmental tobacco pollution exposure. A 25% decrease in employee smoking prevalence was found (21.7% vs 16.2% before vs after policy implementation, respectively). The daily number of cigarettes reportedly smoked by employees who continued smoking and the total number smoked at work decreased across all occupational categories by an average of 25%. Significant reductions were noted in the level of public smoking and the amount of cigarette remnants. Nicotine vapor concentrations decreased significantly in all areas except restrooms. These findings suggest that visible smoking and environmental tobacco smoke exposure can be markedly decreased by instituting a policy eliminating smoking in a large medical center.—Authors' abstract

*Johns Hopkins Medical Institutions, 1830 E. Monument St., 8037, Baltimore, MD 21205.

Illness severity and costs of admissions at teaching and nonteaching hospitals. Iezzoni, L. I.*, Shwartz, M., Moskowitz, M. A., Ash, A. S., Sawitz, E., and Burnside, S.: JAMA 264:1426, 1990.

HEALTH CARE COSTS

This research examined the hypothesis that greater severity of illness explains the higher costs of hospitalizations at teaching compared with nonteaching hospitals. Medical records of 4,439 cases with eight common conditions were reviewed at five tertiary teaching, five other teaching, and five nonteaching hospitals in metropolitan Boston. We assessed acute physiologic status, severity of the principal diagnosis, comorbidities, and functional status. The principal diagnosis was more severe for teaching hospital patients in four conditions, but few significant differences were found for the other severity dimensions by condition. Across all conditions combined, except for functional status, severity was significantly higher at teaching hospitals, but the absolute differences were small. After adjusting for diagnosis related groups, costs were higher at tertiary teaching compared with other teaching and nonteaching hospitals. Further adjusting for severity and other patient characteristics explained 18% (90% confidence interval, 4 to 33) of the higher costs at tertiary compared with nonteaching hospitals.—Authors' abstract

*Division of General Medicine and Primary Care, Department of Medicine, Beth Israel Hospital, 330 Brookline Ave., Boston, MA 02215.

Predicting the appropriate use of carotid endarterectomy, upper gastrointestinal endoscopy, and coronary angiography. Brook, R. H.*, Park, R. E., Chassin, M. R., Solomon, D. H., Keesey, J., and Kosecoff, J.: N. Engl. J. Med. 323:1173, 1990.

MEDICARE, HEALTH CARE COSTS

The authors define a procedure or service as appropriate if its health benefit exceeds its health risk by a sufficiently wide margin that the service or procedure is worth performing. Using this definition, they studied three procedures (coronary angiography, upper gastrointestinal endoscopy, and carotid endarterectomy) in a geographically diverse sample of Medicare patients. They concluded that 17% of the coronary angiographies, 17% of the endoscopies, and 32% of the endarterectomies represented inappropriate overuse. The authors then looked at the specific characteristics of the patients (age, sex, and race), physicians (age, board-certification status, and experience with the procedure), or hospitals (teaching status, profit-making status, and size) to determine whether these correlated with the appropriateness of the procedure. In general, they found that little of the variability in the appropriateness of care could be explained on the basis of standard, easily obtainable data about the patient, the physician, or the hospital. For all three procedures, however, performance in a

teaching hospital increased the likelihood that they would consider the procedure medically appropriate. Angiography was more often performed for appropriate reasons in older or more affluent patients. Being treated by a surgeon who performed many rather than few procedures decreased the likelihood of an appropriate endarterectomy. The authors concluded that appropriateness of care cannot be closely predicted from easily determined characteristics of patients, physicians, or hospitals. They believe that if appropriateness is to be improved it will have to be assessed directly at the level of each patient, hospital, and physician.—Michael A. Kass

*Rand Corporation, 1700 Main St., Box 2138, Santa Monica, CA 90406.

The association of payer with utilization of cardiac procedures in Massachusetts. Weneker, M. B., Weissman, J. S., and Epstein, A. M.*: JAMA 264:1255, 1990.

CARDIAC PROCEDURES, INSURANCE STATUS

To investigate the importance of the payer in the utilization of in-hospital cardiac procedures, we examined the care of 37,994 patients with Medicaid, private insurance, or no insurance who were admitted to Massachusetts hospitals in 1985 with circulatory disorders or chest pain. Using logistic regression to control for demographic, clinical, and hospital factors, we found that the odds that privately insured patients received angiography were 80% higher than uninsured patients; the odds were 40% higher for bypass grafting and 28% higher for angioplasty. Medicaid patients experienced odds similar to those of uninsured patients for receiving angiography and bypass, but had 48% lower odds of receiving angioplasty. In addition, the odds for Medicaid patients were lower than for privately insured patients for all three cardiac procedures. These findings suggest that insurance status is associated with the utilization of cardiac procedures. Future studies should determine the implications these findings have for appropriateness and outcome and whether interventions might improve care.—Authors' abstract

*Department of Health Care Policy, Harvard Medical School, 25 Shattuck St., Parcel B, Boston, MA 02115.

The direct costs of universal precautions in a teaching hospital. Doebbeling, B. N.*, and Wenzel, R. P.: JAMA 264:2083, 1990.

HEALTH CARE COSTS

In 1987, the Centers for Disease Control outlined a policy of universal precautions, a barrier method of minimizing exposure to blood and body fluids. An analysis of the increase in expenditures for barrier isolation materials before and after the institution of universal precautions at the University of Iowa was used to generate a national estimate of the cost of implementing the new guidelines. After the institution of universal precautions, use of rubber gloves at the University of Iowa increased from 1.64 million pairs to 2.81 million pairs annually. A review of hospital purchasing and supply records in both inpatient and outpatient areas indicated that the total annual costs for isolation materials increased by $350,900. This represented an increase from $13.70 to $22.89 per admission after adjustment for inflation. The cost of isolation materials increased from $98 to $215 per 1,000 outpatient visits. Two thirds of the increase was because of rubber gloves and an additional 25% was because of disposable isolation gowns. Universal precautions are estimated to have cost at least $336 million in the United States in fiscal year 1989 after adjustment for inflation. If expenditures for isolation materials at the University of Iowa are representative, previous estimates have significantly underestimated costs nationwide.—Michael A. Kass

*Department of Internal Medicine, C-41 GH, University of Iowa College of Medicine, Iowa City, IA 52242.

Attitudes of internal medicine faculty and residents toward professional interaction with pharmaceutical sales representatives. McKinney, W. P.*, Schiedermayer, D. L., Lurie, N., Simpson, D. E., Goodman, J. L., and Rich, E. C.: JAMA 264:1693, 1990.

PHARMACEUTICAL SALES, PHYSICIAN ATTITUDES

We surveyed faculty and residents from seven hospitals affiliated with three academic internal medicine training programs about their perceptions of the informational and service benefits

vs the risks of ethical compromise involved in interactions with pharmaceutical sales representatives. Questionnaires were returned by 467 (81%) of 575 physicians surveyed. Residents and faculty generally had somewhat negative attitudes toward the educational and informational value of detailing activities at their institutions but indicated that representatives supported important conferences and speakers. Residents were more likely than faculty to perceive contacts with sales representatives as potentially influencing physician decision making. Sixty-seven percent of faculty and 77% of residents indicated that physicians could be compromised by accepting gifts. More than half of the physicians who suggested that such compromise was possible indicated that acceptance of gifts worth more than $100 from drug companies would be likely to compromise a physician's independence and objectivity. A majority of both faculty and house staff favored eliminating presentations by pharmaceutical representatives at their hospitals. Only 10% thought they had had sufficient training during medical school and residency regarding professional interaction with sales representatives.—Authors' abstract

*Medical Service (III), Dallas Veterans Administration Medical Center, 4500 S. Lancaster Rd., Dallas, TX 75216.

Risk of developing a macular hole. Akiba, J., Yoshida, A., and Trempe, C. L.*: Arch. Ophthalmol. 108:1088, 1990.

MACULAR HOLE, VITREOUS TRACTION

Forty-five eyes with early idiopathic macular holes were examined periodically over seven to 87 months (mean follow-up, 32 months). At initial examination, 18 eyes (40%) showed vitreous separation from the fovea. Over the follow-up period, an additional ten eyes (22%) developed vitreous separation. None of these 28 eyes progressed to a fully developed macular hole during follow-up. In contrast, a fully developed macular hole was found in ten of the remaining 27 eyes (37%) without vitreous separation. It is possible that early stage macular holes can be reversed by spontaneous vitreous separation from the fovea.—Michael A. Kass

*Library, Eye Research Institute, 20 Staniford St., Boston, MA 02114.

A longitudinal study of a population based sample of astigmatic children. 1. Refraction and amblyopia. Abrahamsson, M.*, Fabian, G., Andersson, A.-K., and Sjostrand, J.: Acta Ophthalmol. 68:428, 1990.

ASTIGMATISM, AMBLYOPIA, STRABISMUS

The study sample consisted of 310 children who had at least 1 diopter of astigmatism in one or both eyes at 1 year of age. Three years later amblyopia was found in 23 children (7%). Increasing astigmatism during the test period was associated with an increased risk of amblyopia. Most of the children showed a decrease in astigmatism over this three-year period. In contrast in almost every child with amblyopia (visual acuity worse than 20/40) the astigmatism increased or remained unchanged from age 1 to 4 years. Strabismus and oblique astigmatism at any time during the test period were also strongly related to amblyopia. Independent of age, there was no simple relationship between amblyopia and refractive error measured at a single test session.—Michael A. Kass

*Department of Ophthalmology, Sahlgren's Hospital, S-413 45 Göteborg, Sweden.

Staining of the conjunctiva and conjunctival tear film. Eliason, J. A., and Maurice, D. M.*: Br. J. Ophthalmol. 74:519, 1990.

LACRIMAL APPARATUS, CONJUNCTIVA, SULPHORHODAMINE B

Both the distribution of tear fluid over the conjunctiva and any injury to the conjunctival epithelium can be made visible by instilling a fluorescent solution into the eye and observing with an appropriate combination of excitation and barrier filters. Sulphorhodamine B, which has an orange fluorescence that can be separated from the green natural fluorescence of the ocular tissues, gives a greater contrast than fluorescein. The tear film is seen to cover the surface of the conjunctiva and to be concentrated in its folds. Small circular areas of thin tear film appear transiently in the neighbourhood of the limbus after a blink. Occasional cells stain on the normal conjunctiva, particularly in the interpalpebral area. The density of the staining increases in dry eye conditions. Conjunctival trauma is sensitively revealed by the method,

and its healing can be followed. Hard contact lenses are seen to traumatise continually the inferior limbal conjunctiva in symptomless wearers.—Authors' abstract

*Department of Ophthalmology A157, Stanford University Medical Center, Stanford, CA 94305.

Delayed eye and other consequences from exposure to methyl isocyanate. 93% follow up of exposed and unexposed cohorts in Bhopal. Andersson, N.*, Ajwani, M. K., Mahashabde, S., Tiwari, M. K., Kerr Muir, M., Mehra, V., Ashiru, K., and Mackenzie, C. D.: Br. J. Ind. Med. 47:553, 1990.

METHYL ISOCYANATE EXPOSURE, OCULAR IRRITATION, EYELID INFECTION, CATARACT, DECREASED VISUAL ACUITY

A follow-up study three years after exposure to methyl isocyanate in 93% of exposed survivors and in control residents in ten Bhopali communities showed an excess of ocular irritation, eyelid infection, cataract, and a decrease in visual acuity among the exposed group. Analysis of outpatient visits at the Bhopal Eye Hospital demonstrated that exposed individuals had a 40% increased risk of trachoma, a 36% increased risk of other eyelid infections, and a 45% increased risk of irritation of the eye. The "Bhopal eye syndrome" thus begins with superficial interpalpebral erosions of the cornea and conjunctiva that heals within three months. After three years, however, it is now clear that these eyes have an increased incidence of irritation, eyelid infection, and cataract.—Michael A. Kass

*TUC Centenary Institute of Tropical Medicine, London School of Hygiene and Tropical Medicine, London WC1, United Kingdom.

VOLUME 111

FEBRUARY 15

1991

173

Acc 9 7/93

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

• ORIGINAL ARTICLES

Refraction After Radial Keratotomy
Waring, Lynn, Strahlman, Kutner, Culbertson, Laibson, Lindstrom, McDonald, Myers, Obstbaum, Rowsey, Smith, Prospective Evaluation of Radial Keratotomy Study Group

Keratoplasty, Epikeratoplasty, and Keratoconus
Goosey, Prager, Goosey, Bird, Sanderson

Endoscopic Laser-Assisted Lacrimal Surgery
Gonnering, Lyon, Fisher

Intraocular Lens Implantation and Diabetic Retinopathy
Ruiz, Saatci

Delayed-Onset Pseudophakic Endophthalmitis
Fox, Joondeph, Flynn, Pflugfelder, Roussel

Cataract Extraction After Scleral Buckling
Ruiz, Saatci

Fluorophotometric Analysis of Lens Changes
Ogura, Takanashi, Ishigooka, Ogino

Apraclonidine After Cataract Extraction
Wiles, MacKenzie, Ide

Combined Phacoemulsification and Trabeculectomy
Lyle, Jin

Plasminogen Activator Treatment of Subretinal Hemorrhage
Lewis, Resnick, Flannery, Straatsma

Retinal Vasculature in Children With Hypertension
Daniels, Lipman, Burke, Loggie

Optic Neuritis and Visual Recovery
Slamovits, Rosen, Cheng, Striph

Acetazolamide and Abnormal Oculovestibular Response
Hester, Farris

Laser Tomographic Scanner and Optic Nerve Head
Dreher, Tso, Weinreb

Block-Excision of Epithelial Ingrowth
Küchle, Naumann

• PERSPECTIVES

Automated Perimetry in Glaucoma
Joseph Caprioli

• LETTERS TO THE JOURNAL

Microwave thermotherapy for choroidal hemangioma
Finger, Paglione, Packer

Disk neovascularization in chronic anterior uveitis
Pach, Herman, Garrity, Kalina

Retinal vasculitis and Lyme disease
Lang, Schönherr, Naumann

Ulcerative keratitis and Lyme disease
deLuise, O'Leary

Malignant glaucoma after Nd:YAG cyclophotocoagulation
Hardten, Brown

Tissue plasminogen activator for fibrin resolution
Tripathi, Tripathi, Park, Quaranta, Steinsapir, Lehman, Ernest

Corneal ulcer and crack cocaine
Zagelbaum, Tannenbaum, Hersh

Ketoprofen in the treatment of scleritis
Medway, Donzis, Donzis

Scleral ulcer repair
Lin, Wu, Chen, Huang

Retained Veirs rod and canaliculitis
Becker

AIO®

Give yours it



NSAID from Alcon Surgical: PROFENAL® (suprofen) 1% Sterile Ophthalmic Solution — right on target in helping sustain pupillary dilation during cataract surgery.

As challenging as cataract surgery can sometimes be, why risk less than satisfactory intraoperative mydriasis? Let the pupillary stabilizing effect of PROFENAL assist you in reducing the incidence of creeping miosis in your surgery. PROFENAL solution is a sure way to better your chances for being on target with a large pupillary bull's eye case after case.

What it is.

PROFENAL sterile ophthalmic solution from Alcon Surgical is a new nonsteroidal anti-inflammatory drug (NSAID), suprofen 1%, for short-term ophthalmic use. In double-masked, multicenter clinical studies involving over 400 cataract extractions, PROFENAL solution proved to be significantly more effective than placebo in inhibiting intraoperative miosis. Thus, it is an excellent adjunct for surgeons who desire to minimize the dangers and frustrations of pupillary constriction during cataract surgery.

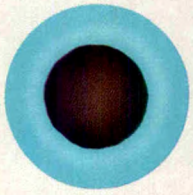
How it works.

Prostaglandins, which are released during intraocular surgery, are believed to exert powerful constricting action on the iris sphincter causing progressive miosis. PROFENAL solution is thought to maintain intraoperative mydriasis by inhibiting the amount of prostaglandins liberated into the aqueous humor.

How it benefits you.

When used adjunctively with cataract surgery-related mydriatic and/or cycloplegic regimens, topically applied PROFENAL ophthalmic solution:

- Helps to sustain a larger intraoperative pupil throughout the case.
- Facilitates removal of crystalline lens nucleus and cortical material.
- Enhances implantation, positioning and/or dialing of posterior chamber IOLs.



Pupil treated with PROFENAL solution maintains a wider aperture, facilitates removal of lens material and eases IOL insertion.

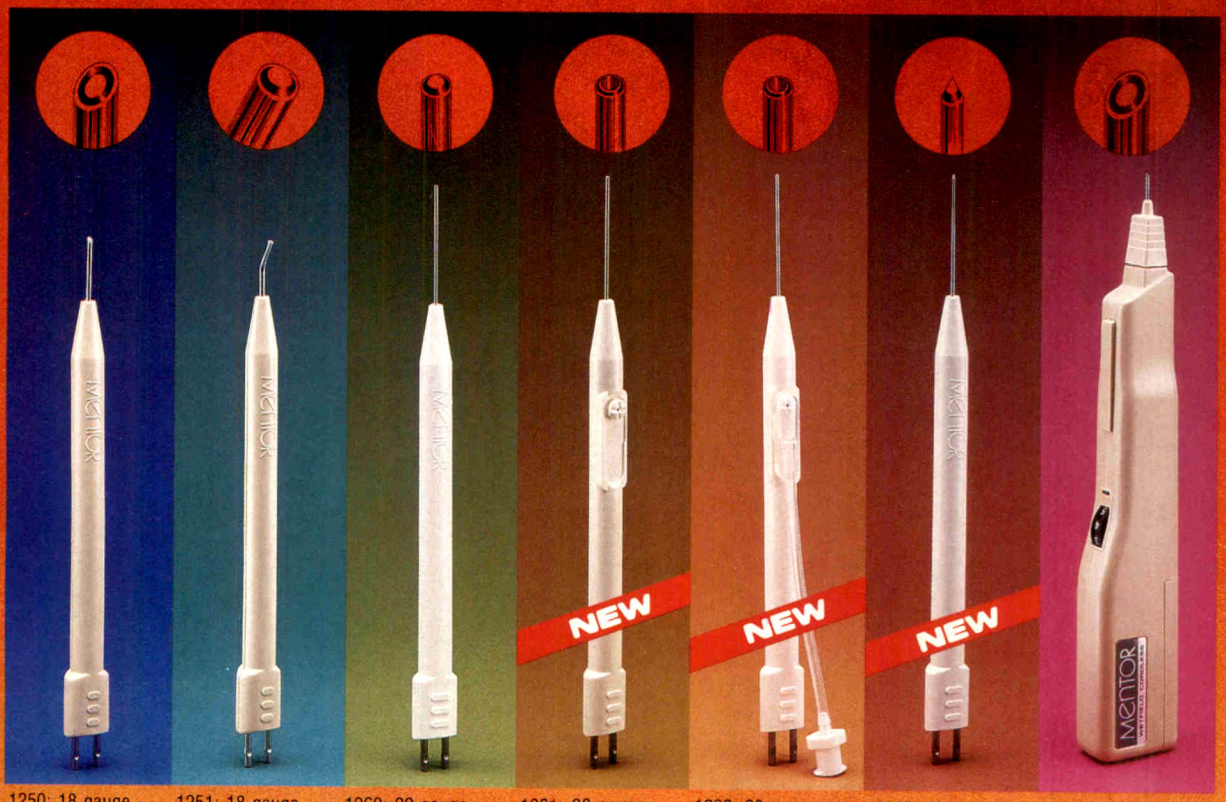
NSAID cautions, contraindications

The potential exists for cross sensitivity to an acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With nonsteroidal anti-inflammatory drugs, the potential exists for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding tendency of ocular tissues in conjunction with ocular surgery.

Clinical studies with acetylcholine chloride revealed no interference and there is no pharmacological basis for

Dependable bipolar hemostasis from the pioneer in WET-FIELD® technology



1250: 18 gauge - efficiency and economy for scleral bleeders.

1251: 18 gauge - same advantages but with 45 degree curved shaft.

1260: 20 gauge - for controlling retinal bleeders.

1261: 20 gauge - retinal hemostasis plus passive aspiration.

1262: 20 gauge - retinal hemostasis plus active aspiration and reflux.

1265: 23 gauge tapered - retinotomies, deep anterior segment bleeders.

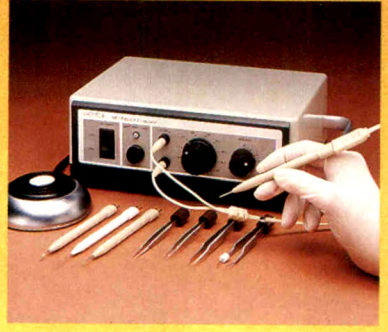
Cordless: 18 gauge - same precision but totally self contained.

Mentor® WET-FIELD Hemostatic Erasers™

Mentor Hemostatic Erasers continue to set new standards for pinpoint hemostasis in both the anterior and posterior segments.

Our years of manufacturing experience are your assurance that safety, reliability and consistency are built into each and every unit.

Two of our newest additions have innovative provisions for passive aspiration and active aspiration and reflux. The third is a 20 gauge tapered to 23 gauge and beveled to a fine point. Now surgeons have all the advantages of bipolar hemostatic control for intraocular procedures.



All Hemostatic Erasers are sold sterile and disposable for ultimate consistency and convenience. They are for use with Mentor WET-FIELD Coagulators including the new portable battery operated WET-FIELD II pictured at left.

For further information or to place an order, write or call toll free:
1-800-992-7557 (National); 1-617-871-6950 (Collect in MA)

Mentor WET-FIELD Hemostatic Erasers were developed in cooperation with Robert C. Drews, M.D., Clayton, Missouri.

Product 1261 was developed in cooperation with F.H. Davidorf, M.D., Columbus, Ohio.

MENTOR O&O INC.

3000 Longwater Drive, Norwell, MA 02061

Hemostatic Eraser is a trademark of Mentor O&O, Inc.
Copyright © 1988, Mentor O&O, Inc.

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 February 1991 Series 3, Vol. 111, No. 2

TABLE OF CONTENTS

ORIGINAL ARTICLES

Stability of refraction during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study
George O. Waring III, Michael J. Lynn, Ellen R. Strahlman, Michael H. Kutner, William Culbertson, Peter R. Laibson, Richard D. Lindstrom, Marguerite B. McDonald, William D. Myers, Stephen A. Obstbaum, J. James Rowsey, Ronald E. Smith, and the Prospective Evaluation of Radial Keratotomy Study Group 133

A comparison of penetrating keratoplasty to epikeratoplasty in the surgical management of keratoconus
John D. Goosey, Thomas C. Prager, Claire B. Goosey, Eugene F. Bird, and James C. Sanderson 145

Endoscopic laser-assisted lacrimal surgery
Russell S. Gonnering, David B. Lyon, and John C. Fisher 152

Posterior chamber intraocular lens implantation in eyes with inactive and active proliferative diabetic retinopathy
Richard S. Ruiz and Osman A. Saatci 158

Delayed-onset pseudophakic endophthalmitis
Gregory M. Fox, Brian C. Joondeph, Harry W. Flynn, Jr., Stephen C. Pflugfelder, and Thomas J. Roussel 163

Extracapsular cataract extraction with intraocular lens implantation after scleral buckling surgery
Richard S. Ruiz and Osman A. Saatci 174

Quantitative analysis of lens changes after vitrectomy by fluorophotometry
Yuichiro Ogura, Taiji Takanashi, Hitoshi Ishigooka, and Nobuchika Ogino 179

Control of intraocular pressure with apraclonidine hydrochloride after cataract extraction
Stephen B. Wiles, Douglas MacKenzie, and Carl H. Ide 184

Comparison of a 3- and 6-mm incision in combined phacoemulsification and trabeculectomy
W. Andrew Lyle and Jia Chi Jin 189

Tissue plasminogen activator treatment of experimental subretinal hemorrhage
Hilel Lewis, Steven C. Resnick, John G. Flannery, and Bradley R. Straatsma 197

The prevalence of retinal vascular abnormalities in children and adolescents with essential hypertension
Stephen R. Daniels, Matthew J. Lipman, Miles J. Burke, and Jennifer M. H. Loggie 205

Visual recovery in patients with optic neuritis and visual loss to no light perception
Thomas L. Slamovits, Carl E. Rosen, Kenneth P. Cheng, and Gerald G. Striph 209

Acetazolamide in the treatment of abnormal oculovestibular response
Ralph B. Hester III and Bradley K. Farris 215

Reproducibility of topographic measurements of the normal and glaucomatous optic nerve head with the laser tomographic scanner
Andreas W. Dreher, Patrick C. Tso, and Robert N. Weinreb 221

Mucogenic secondary open-angle glaucoma in diffuse epithelial ingrowth treated by block-excision
Michael Küchle and Gottfried O. H. Naumann 230

PERSPECTIVES

Automated perimetry in glaucoma
Joseph Caprioli 235

LETTERS TO THE JOURNAL

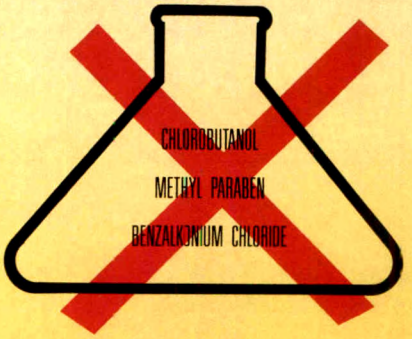
Microwave thermotherapy for choroidal hemangioma. *Paul T. Finger, Robert W. Paglione, and Samuel Packer,* **240. Disk neovascularization in chronic anterior uveitis.** *John M. Pach, David C. Herman, James A. Garrity, and Paul H. Kalina,* **241. Retinal vasculitis with proliferative retinopathy in a patient with evidence of *Borrelia burgdorferi* infection.** *Gabriele E. Lang, Ulrich Schönherr, and Gottfried O. H. Naumann,* **243. Peripheral ulcerative keratitis related to Lyme disease.** *Vincent P. deLuise and Michael J. O'Leary,* **244. Malignant glaucoma after Nd:YAG cyclophotocoagulation.** *David R. Hardten and J. David Brown,* **245. Intracameral tissue plasminogen activator for resolution of fibrin clots after glaucoma filtering procedures.** *Ramesh C. Tripathi, Brenda J. Tripathi, James K. Park, Luciano Quaranta, Kenneth Steinsapir, Erica Lehman, and J. Terry Ernest,* **247. *Candida albicans* corneal ulcer associated with crack cocaine.** *Bruce M. Zagelbaum, Mark H. Tannenbaum, and Peter S. Hersh,* **248. Ketoprofen in the treatment of scleritis.** *David C. Medway, Deborah M. Donzis, and Paul B. Donzis,* **249. Repair of a giant scleral ulcer with a scleral graft and tissue glue.** *Chang Ping Lin, Yuh Hsin Wu, Ming Tsong Chen, and Wen Loong Huang,* **251. Retained Veirs rod and canaliculitis.** *Bruce B. Becker,* **251.**

CORRESPONDENCE

Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture. *Roy S. Rubinfeld, Scott M. MacRae, and Peter R. Laibson,* **253. Reply.** *Harry S. Geggel,* **254. Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome.** *Jay S. Duker and Eric P. Shakin,* **255. Reply.** *David J. Forster, Pravin U. Dugel, George T. Frangieh, Peter E. Liggett, and Narsing A. Rao,* **256. Successful medical management of *Acanthamoeba* keratitis.** *William T. Driebe, Jr., and George A. Stern,*

(Table of Contents continued on Advertising Page 8)





Tears Renewed Ointment™ is Free

Free of Lanolin and Preservatives and Free to You When You Call 1-800-535-7155

Lanolin, obtained from the wool of sheep, and the harsh chemicals in preservatives can cause irritation to someone suffering with dry eye syndrome.

Tears Renewed Ointment™ is dry eye relief. Free of ingredients that can be uncomfortable for your patient.

And priced to save your patient money.

Call today for your free samples.



DIAGNOSE THE PROBLEM.



PRESCRIBE THE RELIEF.



Akorn, Inc.

1-800-535-7155

In Louisiana 1-800-344-2291

100 Akorn Dr. • Abita Springs, LA 70420

Akorn's products are priced to save you money

WE OFFER AN EXTENSIVE LINE OF DIAGNOSTIC AND THERAPEUTIC PRODUCTS.

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 February 1991 Series 3, Vol. 111, No. 2

TABLE OF CONTENTS *(continued from Advertising page 6)*

256. Reply. *Steven T. Berger, Bartly J. Mondino, Richard H. Hoft, and Michael K. Farley,* **257.**

BOOK REVIEWS

Radiology of the Eye and Orbit. Modern Neuroradiology, vol. 4 (Edited by Thomas H. Newton and Larissa T. Bilaniuk). *Reviewed by Melvin G. Alper,* **258. Handbook of Ocular Drug Therapy and Ocular Side Effects of Systemic Drugs (Deborah Pavan-Langston and Edmund C. Dunkel).** *Reviewed by Timothy J. Martin,* **259. Eye Diseases in Hot Climates, ed. 2 (John Sandford-Smith).** *Reviewed by Frank C. Winter,* **259. Cataract Surgery. Alternative Small-Incision Techniques (Edited by George W. Rozakis).** *Reviewed by H. E. Kolder,* **260.**

ABSTRACTS 261

NEWS ITEMS 269

CLASSIFIEDS . . . . . Begins on Advertising 49

COPYRIGHT TRANSFER . . . . . Advertising 22

INSTRUCTIONS TO AUTHORS . . . . . Advertising 39

PRODUCTS AND SERVICES . . . . . Begins on Advertising 44

ADVERTISING INDEX . . . . . Advertising 53

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

LINDA G. CLAUSEN
Records Manager

KAREN D. JOHNSON
Manuscript Editor

MOLLY MELICK
Assistant to the Editor

DIANN J. MARQUIS
Editorial Assistant

MICHAEL J. LUND
Subscription Correspondent

LYNN ANN LINDVIG
AND
RENEE L. KASTAR
Sales and Production

POTASSIUM-RICH, PRESERVATIVE-FREE... MORE LIKE NATURAL TEARS

	Mean Potassium Levels[2]
Human Tears	17 mmol/L
TEARS NATURALE® FREE	16 mmol/L
REFRESH®	0 mmol/L
HypoTears® PF	0 mmol/L

REFRESH® is a registered trademark of Allergan Pharmaceuticals. HypoTears® PF is a registered tradmark of IOLAB Corporation, Pharmaceutical Division.
2. Data on file, Alcon Laboratories, Inc.

PRESERVATIVE-FREE FOR SENSITIVE EYES

- Physiologically more like natural tears
- Comfortable to use – especially for patients with sensitive eyes

UNIQUE DUASORB® SYSTEM MIMICS NATURAL MUCIN

- Patented polymeric system mimics the action of natural mucin
- Creates a strong, stable, more natural tear film layer to protect the corneal surface

FORMULATED FOR MAXIMUM COMFORT

- Low viscosity
- Isotonic
- Same pH as natural tears

RECOMMEND NEW

Tears Naturale® Free

LUBRICANT EYE DROPS

POTASSIUM-RICH, PRESERVATIVE-FREE



Alcon® OPHTHALMIC
ALCON LABORATORIES, INC.
FORT WORTH, TEXAS 76134

© 1991 Alcon Laboratories, Inc.

BRITISH JOURNAL OF OPHTHALMOLOGY

Editorial

705 Photic sneezes *Redmond Smith*

Original articles

706 Photic sneeze reflex in nephropathic cystinosis *Barrett Katz, Ronald B Melles, Michael R Swenson, Jerry A Schneider*

709 When is it safe to stop patching? *John G Oster, John W Simon, Paul Jenkins*

712 Peripheral contrast sensitivity in glaucoma and ocular hypertension *Fernando Falcão-Reis, Eamonn O'Donoghue, Rosaria Buceti, Roger A Hitchings, Geoffrey B Arden*

717 Precapsular film on the aging human lens: precursor of pseudoexfoliation? *Anthony J Dark, Barbara W Streeten*

723 Pathogenesis of corneal oedema associated with herpetic eye disease *William J O'Brien, Julie Guy, Jerry L Taylor*

731 Objective autorefraction in posterior chamber pseudophakia *Palaniswamy Sunder Raj, Tayo Akingbehin, Anthony M Levy*

734 Randomised single blind trial to compare the toxicity of subconjunctival gentamicin and cefuroxime in cataract surgery *C D G Jenkins, P J McDonnell, D J Spalton*

739 Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function *Michael F Marmor*

743 Diode laser trabeculoplasty (DLT) for primary open-angle glaucoma and ocular hypertension *Dominic McHugh, John Marshall, Timothy J ffytche, Peter A M Hamilton, Anthony Raven*

Case reports

748 Atraumatic iris cilia *G I S Mackintosh, M C Grayson*

750 Infectious mononucleosis presenting as bilateral acute dacryocystitis *P L Atkinson, A M Ansons, A Patterson*

751 Infestation of extraocular muscle by *Cysticercus cellulosae David A DiLoreto, Ross A Kennedy, Janet M Neigel, Jack Rootman*

753 **Index**

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

Acc 9 7/93

Stability of Refraction During Four Years After Radial Keratotomy in the Prospective Evaluation of Radial Keratotomy Study

George O. Waring III, M.D., F.A.C.S., Michael J. Lynn, M.S., Ellen R. Strahlman, M.D., Michael H. Kutner, Ph.D., William Culbertson, M.D., Peter R. Laibson, M.D., Richard D. Lindstrom, M.D., Marguerite B. McDonald, M.D., William D. Myers, M.D., Stephen A. Obstbaum, M.D., J. James Rowsey, M.D., Ronald E. Smith, M.D., and the Prospective Evaluation of Radial Keratotomy Study Group

The Prospective Evaluation of Radial Keratotomy Study is a nine-center clinical trial of a standardized technique of radial keratotomy in 435 patients who had simple myopia with a preoperative refraction between −2.00 and −8.00 diopters. We studied the stability of the refractive error during four years after surgery for each of 341 eyes first operated on that had a single surgical procedure. Between baseline and two weeks after surgery, all eyes became less myopic; between two weeks and three months, 161 eyes (59%) lost 1.00 D or more of the initial effect; and between three and six months, 266 eyes (95%) had a stable refraction with less than 1.00 D change.

The change from six months to four years was less than 1.00 D for 246 eyes (72%). There was 1.00 D or more decrease in surgical effect (increased minus power) for 13 eyes (4%), and 1.00 D or more increase in surgical effect (decreased minus power) for 82 eyes (24%). Eyes with larger amounts of preoperative myopia and smaller diameter of the clear zone were more likely to have an increasing effect of the surgery. The duration of this continued increasing effect of the surgery is unknown.

MYOPIA affects approximately 25% of adults in Western countries and an even higher percentage of people in Oriental countries.[1-3] Although spectacles and contact lenses can correct myopia, ophthalmic surgeons have developed surgical techniques during the past 50 years that are intended to correct myopia permanently by altering the shape of the cornea.[4]

Radial keratotomy, the most widely used procedure to correct myopia, has been performed worldwide in hundreds of thousands of patients during the past ten years.[5] If we conservatively estimate that 5% of the 220 million United States citizens have mild to moderate myopia between −2.00 and −8.00 diopters,[2] some 11 million individuals are potentially eligible for the surgery.

The Prospective Evaluation of Radial Keratotomy Study is a nine-center clinical trial funded by the National Eye Institute to determine the outcome of a single standardized radial keratotomy technique. Previous reports at one, three, and four years after surgery have described the level of visual acuity and refractive error achieved, the complications experienced, and the degree of predictability of the surgery.[6-9]

In 1986, Deitz, Sanders, and Raanan[10] described a continued increase in the effect of radial keratotomy, which they designated "progressive hyperopia." Four studies have reported that many eyes demonstrate a continued increase in the effect of surgery of 1.00 D or more between one and four to five years after radial keratotomy: Deitz, Sanders, and Raanan[10] (51 of 165 eyes [31%]); Arrowsmith and Marks[11] (34 of 156 eyes [22%]); Sawelson and Marks[12] (21 of 123 eyes [17%]); and Neumann and associates[13] (31 of 118 eyes [26%]). Deitz, Sanders, and Raanan[14] have updated their observations of operations performed with a diamond knife, reporting that 28 of 149 eyes (19%) demonstrat-

Accepted for publication Oct. 16, 1990.

This study was supported in part by National Eye Institute grants EY03761, EY03756, EY03755, EY03764, EY03753, EY03751, EY03765, EY03767, EY04176, and EY03752.

Reprint requests to George O. Waring III, M.D., Department of Ophthalmology, Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

ed a continued effect of the surgery of 1.00 D or more between one and four years (oral communication, International Society of Refractive Keratoplasty meeting, Las Vegas, Nevada, October 1988).

This continued increase in the effect of the surgery in a substantial portion of the eyes was unanticipated during the early development of radial keratotomy[15] and should be a concern for those considering radial keratotomy as a treatment for myopia. We studied the stability of refraction and the distribution of changes in refractive error that occurred during four years after radial keratotomy in the Prospective Evaluation of Radial Keratotomy Study.

Patients and Methods

We briefly summarize here only the methods that are pertinent to the study of stability and distribution of refraction; additional details have been published previously.[16] The protocol was approved by the institutional review boards of each of the clinical centers. Progress reports were reviewed by a Data and Safety Monitoring Board consisting of ophthalmologists and statisticians not otherwise associated with the study.

Patient selection—Measurements were taken before and after the operation on one eye each of 435 patients who met the following entry criteria: at least 21 years of age; bilateral simple myopia with the spherical equivalent of the cycloplegic refraction between −2.00 and −8.00 D and with 1.50 D or less of refractive astigmatism; visual acuity correctable to 20/20 or better with spectacles; stability of refraction documented by previous clinical records; removal of contact lenses for two weeks before baseline examination with documentation of subsequent stable refraction; absence of active or residual ocular and systemic disease likely to influence corneal wound healing; and signing of informed consent documents.

Surgical technique—Ten specially trained ophthalmic surgeons at nine centers were certified by a performance examination. A single standardized technique was used for all eyes. Incisions were made in the paracentral and peripheral cornea to minimize possible glare problems caused by light scattering from corneal scars. To titrate the amount of correction, the diameter of the uncut circular region or clear zone in the center of the cornea varied with the amount of myopia: −2.00 to −3.12 D = 4.0 mm; −3.25 to −4.37 D = 3.5 mm; and −4.50 to −8.00 D = 3.0 mm. Other aspects of the surgical protocol were the same for all patients.

A round, dull, marking trephine centered on the line of sight delineated the central clear zone of the cornea. The diamond blade of the micrometer knife designed for the study was extended to a length equal to 100% of the thinnest of four intraoperative paracentral ultrasonic corneal thickness readings. The surgeon made eight partial-thickness, freehand radial incisions in the cornea from the edge of the central clear zone mark to the limbal vascular arcade, spaced like the spokes of a wheel, equidistantly around the cornea. After surgery, topical antibiotics were administered for seven days. No topical corticosteroids were used.

Methods of clinical examination—Examination conditions were standardized according to a formal manual of procedures and were monitored during the four-year follow-up by way of site visits and annual recertification courses for the technical staff. At each of the clinical centers, an ophthalmologist-examiner, who was not the surgeon, and a certified technician-coordinator gathered all baseline and postoperative data.

The primary outcome measurement was the spherical equivalent cycloplegic refractive error measured by the technician and verified by the ophthalmologist without reference to previous records.

We characterized the refractive outcome at four years as undercorrected if there was residual myopia greater than −1.00 D and as overcorrected if there was induced hyperopia greater than +1.00 D. We referred to changes in refraction after radial keratotomy as an increase or decrease in the minus power. Increasing minus power was a refractive change in the direction of an increase in myopia or a decrease in hyperopia; decreasing minus power was a refractive change in the direction of a decrease in myopia or an increase in hyperopia. Since radial keratotomy reduces myopia, a reduction in minus power implies a continued increase in the effect of the surgery.

Visual acuity was measured at 4 m with high-contrast, retroilluminated, National Eye Institute visual acuity charts[17,18] in a room with standardized illumination. Patients were examined before surgery and at two weeks, three months, six months, and annually for four years after the operation.

Statistical analysis—We used two criteria to

characterize the stability of the refractive error in each eye: the overall change from six months to four years and the maximum interim change between any two visits. We chose 1.00 D as the minimal amount of clinically meaningful change in refractive error for any time interval after the operation.

The criteria for stability of refraction were calculated as follows. For overall change in refractive error, each eye was assessed with a simple linear regression line that related the cycloplegic refraction at the follow-up visits to the time after surgery, beginning with the six-month visit. Patients who did not have at least four of the five examinations between six months and four years were not included in this study. The estimated slope of the regression line was then used to estimate the trend of the refractive change between six months and four years. The largest change in refraction between any two, not necessarily consecutive, examinations was calculated as the maximum interim change. This criterion was included as an assessment of stability of refraction because patients had a large change in refractive error between individual visits without having a clear trend over the four years.

Using these two criteria, patients were classified into four categories that characterized the stability of their refractive error: stable, less than 1.00 D of change according to both criteria; fluctuating, less than 1.00 D of change according to the regression criteria, but a maximum change between any two visits of 1.00 D or more; increasing effect, 1.00 D or more of change in both criteria in a direction of decreased minus power; loss of effect, 1.00 D or more of change in both criteria in a direction of increased minus power.

To examine factors that were potentially related to the refractive change from six months to four years, the four categories of stability were compared with respect to preoperative factors (age, intraocular pressure, diameter of central clear zone, corneal thickness, and average central keratometry) and postoperative factors (depth of incision scar and the spherical equivalent cycloplegic refractive error at two weeks, three weeks, and six months). Comparisons were done using analysis of variance or chi-square tests, depending on whether the factor was quantitative or categoric. All eyes had eight incisions, so this variable could not be studied. We also measured the absolute change in refraction from baseline to two weeks, two weeks to three months, three months to six months, and six months to four years.

Refractive stability for fellow eyes—To establish a standard of comparison for the change in myopia over time, we examined the fellow eyes of patients in this study. Measurements were taken on the unoperated on eye at the initial preoperative visit and at the visit one year after surgery on the first operated on eye. To evaluate the change under as standardized conditions as possible, we included only eyes examined by the same clinical coordinator in the same examining room at both times. Patients wearing a contact lens (which could warp the cornea) on the unoperated on eye during the year between examinations were excluded.

Refractive stability for eyes with a repeated radial keratotomy—We analyzed separately the eyes that had a repeated radial keratotomy, using the same methods as for eyes with a single operation. The refractive data at three months, and at one, two, three, and four years after the second operation were used.

Results

Study population—The study design specified a sample size of 400 eyes to estimate the percentage of patients that would have a residual refractive error within 1.00 D of emmetropia, with a precision of approximately 5%. Surgery was performed on the first eye of 435 patients, aged 21 to 58 years (mean, 33 years; standard deviation, 7 years), between March 1982 and October 1983. Each of the nine clinical centers entered 43 to 50 patients. The results for the first operated on eye of each patient are given. Of the 435 eyes, the numbers of eyes examined at the postoperative intervals were the following: six months, 430 eyes (99%); one year, 424 eyes (98%); two years, 405 eyes (93%); three years, 416 eyes (95%); and four years, 397 eyes (91%).

Of these 435 eyes, 62 (14%) underwent a second radial keratotomy operation and were analyzed separately. Of the 373 eyes with a single operation, 17 eyes had clinical occurrences that altered the outcome of the surgery[7] and 15 eyes did not have at least four of the five follow-up examinations between six months and four years. Therefore, the primary results include 341 eyes that received a single radial keratotomy operation and were followed up for four years. Additionally, we studied the stabili-

ty of refractive error in eyes that had a repeated radial keratotomy.

Refractive stability in fellow eyes—The change in refraction during one year for 156 fellow eyes was less than 0.25 D for 68 eyes (44%). No eye changed 1.00 D or more; 43 eyes (27%) had an increase in minus power of 0.25 to 0.75 D; and 45 eyes (29%) had a decrease in minus power of 0.25 to 0.88 D. Based on these results and clinical judgment, we chose 1.00 D as an indicator of a clinically meaningful change in refractive error.

Early postoperative stability of refraction—We focused on the refractive stability during six months to four years after surgery. We also, however, studied the early refractive changes during the first six months for these 341 eyes.

There were 333 of the 341 eyes examined at two weeks after surgery. All of these 333 eyes became less myopic between baseline and two weeks (Fig. 1, top). The average refractive change was a decrease in myopia of 4.83 D (standard deviation, 1.61 D; range, 1.75 to 10.75 D). During this time many patients reported instability of visual acuity during the day and from one day to the next.

Of the 341 eyes, 273 had a cycloplegic refraction approximately three months after surgery. Most of these 273 eyes lost some effect of the surgery between two weeks and three months (Fig. 1, bottom). The average refractive change was an increase in minus power of 1.24 D (standard deviation, 0.83 D); 161 of 273 eyes (59%) lost 1.00 D to 4.00 D of effect. Only eight of 273 eyes (2%) had a decrease in minus power, ranging from 0.12 D to 0.75 D. There was a tendency for those eyes having a larger initial reduction of myopia from baseline to two weeks to have a larger regression of surgical effect from two weeks to three months (correlation, 0.4; Fig. 1, bottom).

There was no overall trend in refractive change between three months and six months (Fig. 1, bottom). The average change for 281 of the 341 eyes examined at both three and six months after surgery was 0.01 D; and 266 of 281 eyes (95%) changed by less than 1.00 D. Seven of 281 eyes (2.5%) had an increase and eight of 281 eyes (2.5%) had a decrease in minus power between 1.00 and 1.88 D.

Changes in refraction from six months to four years after surgery—We estimated the overall stability of refraction by determining the number of eyes that changed by 1.00 D or more (Fig. 2). We also calculated the average change for the 341 eyes, which was +0.41 D (standard deviation, 0.69 D; range, −1.81 to +3.61 D). The average refraction at each postoperative interval gave a crude indication of the overall trend toward hyperopia: six months, −0.33 D; one year, −0.18 D; two years, −0.03 D; three years, +0.05 D; and four years, +0.11 D.

The two criteria for determining the categories of refractive stability are the overall change estimated by the slope of the simple linear regression line and the maximum interim change between any two examinations between six months and four years. Using a 1.00-D value as an indication of instability of refraction for both criteria, there were four categories of refractive change among the eyes. Figure 3 shows one example in each of the four categories.

The refractive categories are defined as follows: Category 1, Stable refraction: For 197 of 341 eyes (58%), there was less than 1.00 D of refractive change according to both stability criteria. The mean refractive change in this category was +0.19 D (standard deviation, 0.36 D). The distribution of the refractive error was similar at six months and four years (Table 1).

Category 2, Fluctuating refraction with no definite trend: For 49 of 341 eyes (14%), there was a maximum change of 1.00 D or more between two of the five examinations, but the overall change calculated from the regression line was less than 1.00 D. The change was a decrease in minus power for 35 eyes and an increase in minus power for 14 eyes. In this category the number of eyes overcorrected by more than 1.00 D increased from seven eyes (14%) at six months to 12 eyes (25%) at four years (Table 1). Since the overall change in refraction was less then 1.00 D, the overall refractive outcome in these eyes was considered stable. Combining this category with Category 1, we considered a total of 246 of 341 eyes (72%) to be stable.

Category 3, Increasing effect of surgery: For 82 of 341 eyes (24%) there was a change of 1.00 D or more in the direction of decreased minus power by both criteria, which indicated an increasing effect of the surgery. The mean refractive change was 1.28 D (standard deviation, 0.52 D). In this category, the number of undercorrected eyes decreased from 24 (29%) at six months to three (4%) at four years, whereas the number of overcorrected eyes increased from 12 (15%) at six months to 36 (44%) at four years (Table 1).

To determine the effect of the continued increase in effect on the refractive outcome, we classified the 82 eyes in Category 3 according to

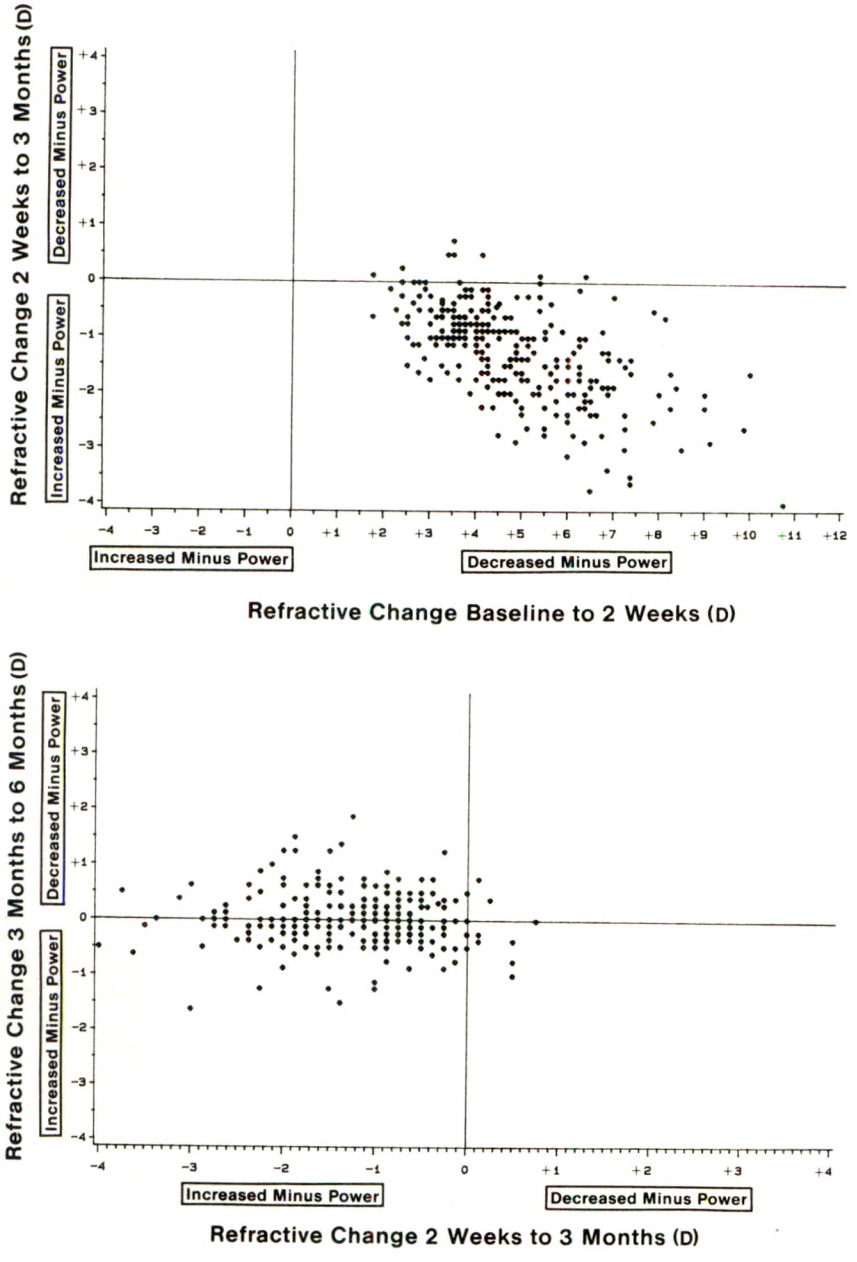


Fig. 1 (Waring and associates). Scattergrams of change in refraction between baseline and three months. Top, The refractive change between baseline and two weeks after surgery compared with that between two weeks and three months after surgery. All eyes had a reduction in myopia at two weeks after surgery. Most eyes lost some effect between two weeks and three months after surgery. Eyes that had a greater refractive change at two weeks tended to have a greater loss of effect between two weeks and three months (correlation, 0.4). Bottom, The refractive change between two weeks and three months compared with that between three months and six months after surgery. There was much less refractive change between three to six months, 147 of 281 eyes (50%) changing by 0.25 diopters or less and only 15 eyes (5%) changing by 1.00 diopter or more. The data points cluster around the no change line between three to six months, which indicates relative stability. (Note the change in the scale of the horizontal axis between the graphs.)

their refractive error at six months and four years. Of these 82 eyes, the 24 eyes (29%) with residual myopia greater than −1.00 D at six months were between −1.00 D and +1.00 D at four years (except for two eyes). Of the 46 eyes (56%) with a refractive error between −1.00 D and +1.00 D at six months, 24 (52%) had a hyperopic refractive error greater than +1.00 D at four years. Finally, 12 (15%) of the 82 eyes had a hyperopic refractive error greater than +1.00 D at six months and were even more overcorrected at four years. Thus, as a result of the continued increase in the effect of surgery in these 82 eyes, 24 eyes (29%) had an improvement in their refractive error, 22 eyes (27%) remained between −1.00 and +1.00 D, and 36 eyes (44%) had a worse refractive error because they had become overcorrected by more than +1.00 D.

Category 4, Loss of surgical effect: A small number of eyes, 13 of 341 (4%), had an overall loss of effect of the surgery (mean, 1.11 D;

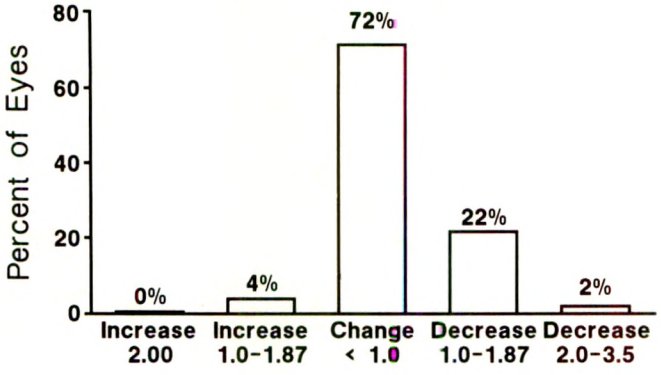


Fig. 2 (Waring and associates). The change in the spherical equivalent of the cycloplegic refraction between six months and four years for 341 eyes.

standard deviation, 0.47 D). In this category, the number of eyes undercorrected by more than −1.00 D increased from four to eight (Table 1).

Refractive error from six months to four years after surgery—The distribution of refractive errors among the 341 eyes with a single operation was divided into three groups: undercorrected (more than −1.00 D); overcorrected (more than +1.00 D); and the remainder between −1.00 D and +1.00 D. These three groups were compared at six months and four years after surgery and showed an overall change in the hyperopic direction (Table 2).

Of the 82 eyes that were undercorrected at six months after surgery, only 45 eyes (55%) remained undercorrected at four years; none became overcorrected more than +1.00 D. Of the 220 eyes that had a refractive error between −1.00 D and +1.00 D at six months after surgery, 166 eyes (75%) remained in this category at four years. Of the 39 eyes that were overcorrected six months after radial keratotomy, 32 eyes (82%) were still overcorrected at four years.

Rate of change in refraction—The number of eyes that changed by 1.00 D or more increased progressively from six months to four years (Table 3). Thus, it was not possible to determine from these data when the refraction will be likely to stabilize for individual eyes. The rate of change in refraction for eyes exhibiting instability was slow, most showing less than one diopter of change during any one-year period.

Factors that affected stability of refraction—To identify the factors associated with a change in refraction, we compared the four stability categories with respect to the preoperative, surgical, and early postoperative factors listed in the Patients and Methods section. The eyes that were unstable had a significantly smaller diameter of the central clear zone and therefore longer incisions than the eyes that were stable ($P = .00004$). However, since the diameter of the central clear zone was determined by the level of preoperative myopia, either of these two factors or their combination could be responsible for the observed result. No other preoperative or surgical variable correlated significantly with change in refraction.

TABLE 1
NUMBER OF EYES IN EACH INTERVAL OF REFRACTIVE ERROR AT SIX MONTHS AND FOUR YEARS ACCORDING TO REFRACTIVE STABILITY CATEGORY

		REFRACTIVE ERROR AT 6 MONTHS AND 4 YEARS					
		< − 1.00 D		± 1.00 D		> + 1.00 D	
REFRACTIVE STABILITY CATEGORY	TOTAL NO. OF EYES	6 MONTH NO. (%)	4 YEAR NO. (%)	6 MONTH NO. (%)	4 YEAR NO. (%)	6 MONTH NO. (%)	4 YEAR NO. (%)
Stable	197	40 (20)	30 (15)	139 (71)	146 (74)	18 (9)	21 (11)
Fluctuating	49	14 (29)	10 (20)	28 (57)	27 (55)	7 (14)	12 (25)
Increased effect	82	24 (29)	3 (4)	46 (56)	43 (52)	12 (15)	36 (44)
Loss of effect	13	4 (31)	8 (61)	7 (54)	4 (31)	2 (15)	1 (8)
Total	341	82 (24)	51 (15)	220 (65)	220 (65)	39 (11)	70 (20)

TABLE 2
COMPARISON OF THE NUMBER AND PERCENT OF EYES IN EACH INTERVAL OF REFRACTIVE ERROR AT SIX MONTHS AND FOUR YEARS AFTER SURGERY

	REFRACTION AT FOUR YEARS		
REFRACTION AT SIX MONTHS	UNDERCORRECTED (< −1.00 D) NO. (%)	−1.00 TO +1.00 D NO. (%)	OVERCORRECTED (> +1.00 D) NO. (%)
Undercorrected (< −1.00 D)	45 (55)	37 (45)	0
−1.00 to +1.00 D	21 (10)	166 (75)	33 (15)
Overcorrected (> +1.00 D)	4 (10)	3 (8)	32 (82)
Total	70 (21)	206 (60)	65 (19)

TABLE 3
EYES* WITH DECREASING MINUS POWER ≥ 1 D BETWEEN FOLLOW-UP VISITS AFTER RADIAL KERATOTOMY

	TO 1 YEAR	TO 2 YEARS	TO 3 YEARS	TO 4 YEARS
From 6 months	18 (5.3%)	41 (12.3%)	50 (14.9%)	72 (22.6%)
From 1 year	—	18 (5.4%)	31 (9.3%)	46 (14.5%)
From 2 years	—	—	14 (4.3%)	21 (6.8%)
From 3 years	—	—	—	13 (4.2%)

*The total number of eyes for each of the follow-up intervals varied from 311 to 340.

Changes in refraction and corneal power—To document that the changes in refraction were caused by changes in the curvature and power of the cornea, we correlated the change in the average central keratometry measurements with the change in the spherical equivalent cycloplegic refraction between six months and four years. The correlation between the two was −0.52 (P = .001), which indicated a moderate association.

Stability of refraction after repeated radial keratotomy—Of the 62 eyes with reoperations, 42 had at least four follow-up visits between three months and four years after the repeated radial keratotomy. We categorized the 42 eyes with a second radial keratotomy into the same four stability categories used for the eyes with a single operation: (1) stable refraction, 27 eyes (64%); (2) fluctuating refraction with no definite trend, six eyes (14%); (3) increasing effect of surgery, seven eyes (17%); and (4) loss of surgical effect, five eyes (17%). These percentages were not significantly different from those for the eyes operated on once (P = .6).

The average change in refraction from six months to four years for the eyes with a repeated operation was +0.39 D (standard deviation, 0.87 D), which was not statistically significantly different from the mean for eyes with single operation, +0.43 D (standard deviation, 0.70 D).

Discussion

During the past decade of development of radial keratotomy in the United States, considerable information has been published about surgical techniques, efficacy, predictability, and safety of the operation. Improvements in preoperative planning and surgical techniques have produced better refractive results in studies performed during the later 1980s[14,19,20] than those performed in the early to mid 1980s.[8,11,12,21] Salz and associates[19] reported a series of 112 consecutive eyes with preoperative refractions between −1.12 D and −4.25 D that received an initial four-incision radial keratotomy followed by an additional four incisions in 15 eyes (13%). A postoperative refraction of ±1.00 D was achieved in 101 eyes (90%) at three to 48 months after surgery. Similarly, Spigelman, Williams, and Lindstrom[20] reported a series of 32 eyes with a baseline refraction between −1.50 D and −4.75 D using a four-incision radial keratotomy without repeated operations. The refraction was within ± 1.00 D in 29 eyes (91%) at one year after surgery. Despite these improving results, the ability to predict the refractive and visual acuity outcome for a particular eye is less accurate than surgeons and patients desire. For example, the 90% prediction interval for refractive change after surgery in 390 eyes with preoperative refractions of −2.00 D to −8.00 D in the Prospective Evaluation of Radial Keratotomy Study four years after surgery was 4.50 D wide.[8]

If these refractive results remain stable over time, ophthalmologists and patients with myopia will have a reasonable basis on which to base expectations about radial keratotomy. Many eyes, however, do not retain a stable refraction after radial keratotomy.[8,10-13,15]

This report confirms the findings of four other studies[10-13] that approximately one in five eyes had an increasing effect of the surgery of 1.00 D or more in the hyperopic direction during four to five years after radial keratotomy (Table 2).

Four kinds of change in refraction occur after radial keratotomy: changes in the first few weeks that are an early response to the surgery (Fig. 1); irregular fluctuation from day-to-day or from month-to-month over a period of years; a gradual trend in one direction, usually the hyperopic direction, over a period of years; and variation from morning to evening, diurnal fluctuation.[22-26]

Refractive change in myopic eyes—Studies of the natural course of myopia in the range of −2.00 to −8.00 D (the range selected in this study) indicate that there is little change in the refractive error after the patient reaches age 21 years. Brown[27] found that between age 20 and 33 years, the increase in myopia had a low yearly average of 0.04 diopters. In this study, we found that fellow eyes changed less than 1.00 D during a one-year interval. We also reported[28] that of 88 unoperated on eyes followed up for four to 5½ years, 64 eyes (73%) changed refraction by less than 1.00 D and the remainder became 1.00 D to 2.50 D more myopic. None became less myopic. Therefore, the increase in effect of radial keratotomy over time can be attributed to the surgery. We and others[10-12] define a meaningful change of refraction as 1.00 D or more between two time points. This amount of change would be noticed by most patients and would usually require new spectacles or contact lenses.

Changes in refraction during the first six months after surgery—A dramatic reduction in myopia occurred in all eyes after surgery and persisted at the first data collection point at two weeks. Many patients remarked that they could see clocks and recognize faces at distance for the first time in their memory. Most of the eyes showed some loss of this initial effect by three months; the mean change was an increase in myopia of 1.24 D (Fig. 1). McDonnell and Schanzlin[29] found a similar regression of effect in the first three months after surgery.

In general, the refraction was stable by three months, only 15 eyes (5%) showing a change in refraction of 1.00 D or more from three to six months. Thus, the overall reported outcome of radial keratotomy can be determined between approximately six to 12 weeks after surgery. The ophthalmologist and the patient can plan further surgery or optical correction at this time. Results of studies can be reported at three to six months, instead of the commonly used 12 months, allowing earlier judgments about the initial efficacy of different techniques of radial keratotomy.

Changes in refraction from six months to four years after surgery—We found that 49 (14%) of the 341 eyes demonstrated at least 1.00 D of up-and-down fluctuation in refraction during the four-year follow-up, even though the overall refractive change from six months to four years was less than 1.00 D (mean, 0.26 D; standard deviation, 0.50 D) (Table 1; Fig. 3). Although the fluctuation may bother patients, we did not consider it as unstable if the overall change in refraction between six months and four years was less than 1.00 D. Thus, we considered 246 of 341 eyes (72%) stable during this interval (Fig. 2).

The most significant finding was that 82 of 341 eyes (24%) showed a continued increase in effect of the surgery with a change in refraction in the hyperopic direction (a decrease in minus power). This phenomenon was unanticipated in the early development of radial keratotomy,[15] and it represents one of its unsolved problems. Four other studies have also described this effect (Table 2).[10-13]

How long the increasing effect of the surgery will last is unknown. This study demonstrates a cumulative effect over four years. Neumann and associates[13] showed that the change between one and three years (mean, +0.27 D) was the same as between three and five years (mean, +0.30 D). Ivanova and Fyodorov have reported a cumulative increasing effect of the surgery over 12 years in a series of cases performed in the Soviet Union (P. Ivanova, M.D., and S. N. Fyodorov, M.D., oral communication, 2nd International Cataract Implant Microsurgical and Refractive Keratoplasty Conference, Nygoya, Japan, July 1–3, 1988).

Consequences of refractive instability—The finding of an increasing effect of radial keratotomy has a number of practical consequences. The total number of patients who gradually become hyperopic after radial keratotomy will increase (Table 1). Of the 82 eyes that showed a continued effect of the surgery, only 12 eyes (15%) were overcorrected by 1.00 D or more at six months, but 36 eyes (44%) were overcorrected at four years after surgery.

Symptomatic presbyopia will occur earlier than usual. Most patients with emmetropia and hyperopia must use plus lenses in the form of reading spectacles or bifocals after approximately age 45 years to achieve satisfactory near vision. Persons with hyperopia will have an earlier need for reading spectacles. We have the impression that most patients who have had radial keratotomy and become presbyopic in

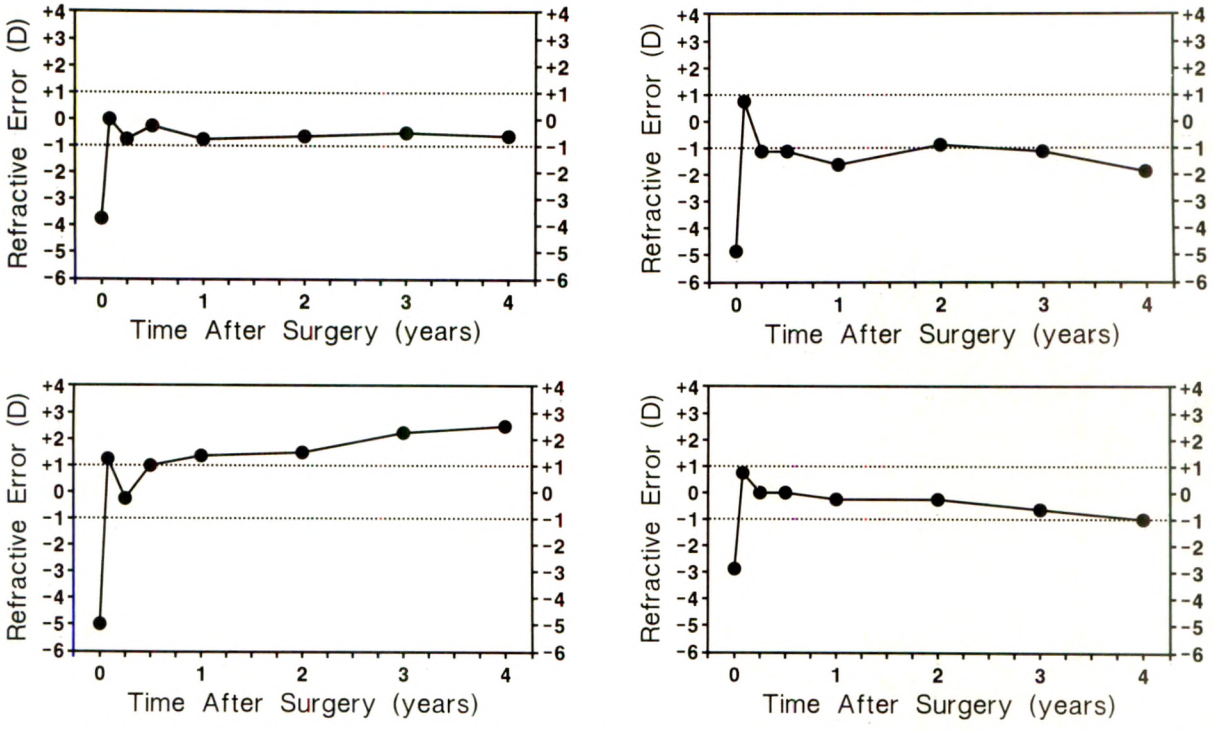


Fig. 3 (Waring and associates). Examples of patterns of refractive change. Top left, Stable course. Of 341 eyes, 197 (58%) changed by less than 1.00 diopter. Top right, Fluctuation. Of 341 eyes, 49 (14%) did not have a definite trend but did have a change of 1.00 diopter or more during some follow-up interval. Bottom left, Continued effect of surgery. Of 341 eyes, 82 (24%) had a decrease in minus power of 1.00 diopter or more. Bottom right, Loss of effect of surgery. Of 341 eyes, 13 (4%) had an increase in minus power of 1.00 diopter or more.

their early 40s are happy to have exchanged the full-time use of their distance correction for part-time use of reading spectacles.

Many patients whose eyes are undercorrected after surgery will perceive the increase in the effect of the surgery as a positive advantage because the decreasing residual myopia results in an improved distance visual acuity.

Instability of refraction decreases the predictability of the outcome. In the Prospective Evaluation of Radial Keratotomy Study four years after surgery, the 90% prediction interval for the refractive outcome was 4.42 D wide,[8] approximately eight times greater than that achieved by fitting spectacles or contact lenses (0.50 D). The inability to identify preoperatively the individuals who will exhibit an increasing effect of the surgery makes it more difficult to predict the outcome of surgery for an individual patient.

The rate of change of refraction three months or more after surgery is slow, obviating concern over abrupt, disruptive changes in visual function. For example, the 82 eyes that showed an increasing effect of the surgery from six months to four years had a total mean change of 1.28 D, a rate of 0.03 D per month. None reported sudden changes in visual function. This is especially important for individuals with professions that require good visual acuity for proper function, such as law enforcement, firefighting, and the performing arts.

A mild residual myopia of −0.50 D to −1.00 D is a more desirable surgical result than emmetropia. This residual low myopia allows patients to retain good uncorrected visual acuity,[30] delays the onset of symptomatic presbyopia, and hedges against an increase in the effect of the surgery. Methods of achieving this intentional mild undercorrection include using the patient's age as a preoperative variable, doing less extensive surgery in older individuals, using four incisions, and avoiding incisions that are nearly 100% of corneal thickness.

Mechanisms of refractive instability—The mechanisms of instability of refraction both in the early postoperative period and during many years after surgery is unknown. We found no distinctive preoperative characteristics that identified individuals likely to have an unstable

refraction, a conclusion similar to that reached by Deitz, Sanders, and Raanan[10] and by Sawelson and Marks.[12] Although we found a statistically significant correlation with smaller diameter clear zones and Sawelson and Marks[12] found a correlation with deeper incisions, there is no clear-cut way to predict instability of refraction in individual eyes.

The loss of initial effect that occurs in the first few weeks after surgery probably reflects a change in stromal hydration. Stromal edema produces greater gaping of the control corneal incisions and greater flattening of the central corneal, which enhances the effect of the surgery. As the epithelium fills the keratotomy incisions and reestablishes its barrier function, more normal corneal hydration is restored, which decreases the initial effects of the surgery. Once equilibrium is reached, refraction remains more stable. It is probable that the physiologic stromal edema that occurs during sleep is responsible for the diurnal variation in refraction in which the cornea is flatter upon awakening and becomes steeper during the day.[22-24]

Laboratory models have demonstrated that corneal edema induces large changes in refraction immediately after surgery. For example, Parel, Simon, and Lowery[31] showed that eyes flooded with balanced salt solution had an induction of more than 10.0 D of astigmatism after transverse keratotomy and 5.00 D of flattening after radial keratotomy. When the surface of the corneas was covered with dextran or silicone oil, however, no change greater than 1.00 D was recorded. Presumably the balanced salt solution produced marked swelling of the stroma within the incisions, causing greater incision gape and a greater change in curvature, whereas the dextran and silicone produced less stromal swelling and therefore essentially no measurable change in central corneal curvature.

The major variable affecting long-term refractive stability is probably the slow healing of the unsutured avascular incision. It contains an epithelial plug that is extruded over a period of a few years and is replaced by new extracellular matrix and cicatricial tissue that contains mild fibroblasts over a span of approximately five years.[32-34] Other forces also tend to flatten the central cornea, including the pressure of the eyelids with each blink,[35] increased atmospheric pressure, and increased intraocular pressure,[36] but their role in long-term stability is unknown.

TABLE 4
STUDIES OF STABILITY OF REFRACTION* AFTER RADIAL KERATOTOMY

STUDY	NO. OF EYES	FOLLOW-UP (YRS)	CHANGE < 1 D NO. (%)	DECREASE MINUS POWER ≥ 1 D NO. (%)
Prospective Evaluation of Radial Keratotomy	317	1–4	263 (83)	46 (15)
Deitz, Sanders, and Raanan[10]	165	1–4	107 (65)	51 (31)
Arrowsmith and Marks[11]	156	1–5	109 (70)	34 (22)
Sawelson and Marks[12]	123	1.5–5	96 (78)	21 (17)
Neumann and associates[13]	118	1–5	81 (69)	31 (26)

*Spherical equivalent refraction.

The major remaining unknown about radial keratotomy for myopia is the long-term stability of refraction. It is unknown how long the general trend of an increase in the effect of the surgery will last, and it is unknown how many patients will be affected by this trend. Published data extend only to five years (Table 4), and there is a need for long-term follow-up to document whether this is a persistent effect that can last for decades and affect an increasingly large number of patients or whether it is limited to only a certain population and stops at some point in time.

PROSPECTIVE EVALUATION OF RADIAL KERATOTOMY STUDY CURRENT INVESTIGATORS

Bascom Palmer Eye Institute (University of Miami School of Medicine, Miami, Florida); Principal Investigator: William Culbertson, M.D.; Coordinator: Millie Espinal.

Emory University (Atlanta, Georgia); Principal Investigator: George O. Waring III, M.D.; Coordinator: Mary C. Gemmill, C.O.M.T.

Louisiana State University Eye Center (New Orleans, Louisiana); Principal Investigator: Marguerite B. McDonald, M.D.; Investigators: Herbert E. Kaufman, M.D., Bruce A. Barron, M.D.; Coordinator: Deborah Poloson, L.D.O.

University of Minnesota (Minneapolis, Minnesota); Co-principal Investigators: Richard L. Lindstrom, M.D., and Donald J. Doughman, M.D.; Investigators: J. Daniel Nelson, M.D.; Coordinator: Patricia Williams, C.O.T.

Mount Sinai School of Medicine (New York, New York); Principal Investigator: Stephen A. Obstbaum, M.D.; Investigators: Penny A. Asbell, M.D., Stephen M. Podos, M.D.; Coordinator: Norma Justin, C.O.A.

University of Oklahoma (McGee Eye Institute, Oklahoma City, Oklahoma); Principal Investigator: J. James Rowsey, M.D.; Investigators: Hal D. Balyeat, M.D., Mark A. Terry, M.D.; Coordinator: Janie Shofner, C.O.A.

University of Southern California (Estelle Doheny Eye Foundation, Los Angeles, California); Principal Investigator: Peter J. McDonald, M.D.; Investigators: James J. Salz, M.D., Ronald E. Smith, M.D., Douglas L. Steel, M.D., Richard A. Villasenor, M.D., and Linda B. Bourque, Ph.D.; Coordinator: Jenny Garbus, C.O.T.

William Beaumont Eye Clinic (Royal Oak, Michigan); Principal Investigator: William D. Myers, M.D.; Investigators: John W. Cowden, M.D., Paul Fecko, M.D., Robert L. Stephenson, M.D.; Coordinator: Vicki Roszka-Duggan, C.O.T.

Wills Eye Hospital (Philadelphia, Pennsylvania); Principal Investigator: Peter R. Laibson, M.D.; Investigators: Juan A. Arentsen, M.D., Michael A. Naidoff, M.D., Elisabeth A. Cohen, M.D.; Coordinator: Nubia Richman, C.O.

Study Chairman: George O. Waring III, M.D., Emory University, Atlanta, Georgia.

Statistical Coordinating Center, Emory University, Department of Epidemiology and Biostatistics (Atlanta, Georgia); Co-principal Investigators: Michael J. Lynn, M.S., and Michael H. Kutner, Ph.D.; Investigators: Azhar Nizam, M.S., and Brooke Fielding, M.S.

Clinical Monitors: Jay H. Krachmer, M.D., James P. McCulley, M.D., and Walter J. Stark, M.D.

Data and Safety Monitoring Board: Chairman: Richard A. Thoft, M.D.; Members: James V. Aquavella, M.D., Jules L. Baum, M.D., Robert J. Hardy, Ph.D., Jay A. Krachmer, M.D., Aran Safir, M.D., Robert D. Sperduto, M.D., Joel Sugar, M.D., and James Ware, Ph.D.

National Eye Institute: Robert D. Sperduto, M.D., Ralph J. Helmsen, Ph.D., and Richard Mowery, Ph.D.

References

1. Curtin, B. J.: The Myopias. Basic Science and Clinical Management. Philadelphia, Harper & Row, 1985, pp. 39–60.
2. Sperduto, R. D., Seigel, D., Roberts, J., and Rowland, M.: Prevalence of myopia in the United States. Arch. Ophthalmol. 101:405, 1983.
3. Leibowitz, H. M., Krueger, D. E., Maunder, L. R., Milton, R. C., Kini, M. M., Kahn, H., Nickerson, R. J., Pool, J., Colton, T. L., Ganley, J. P., Lowenstein, J. I., and Dawber, T. R.: The Framingham eye study monograph. An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975. Surv. Ophthalmol. 24:476, 1980.
4. Waring, G. O.: Making sense of keratospeak. Arch. Ophthalmol. 103:1472, 1985.
5. ———: Refractive Keratotomy for Myopia and Astigmatism. St. Louis, C. V. Mosby. In press.
6. Waring, G. O., Lynn, M. J., Gelender, H., Laibson, P. R., Lindstrom, R. L., Myers, W. D., Obstbaum, S. A., Rowsey, J. J., McDonald, M. B., Schanzlin, D. J., Sperduto, R. D., Bourque, L. B., and the PERK Study Group: Results of the prospective evaluation of radial keratotomy (PERK) study one year after surgery. Ophthalmology 92:177, 1985.
7. Waring, G. O., Lynn, M. J., Culbertson, W., Laibson, P. R., Lindstrom, R. D., McDonald, M. B., Myers, W. D., Obstbaum, S. A., Rowsey, J. J., Schanzlin, D. J., and the PERK Study Group: Three-year results of the prospective evaluation of radial keratotomy (PERK) study. Ophthalmology 94:1339, 1987.
8. Waring, G. O., Lynn, M. J., Fielding, B., Asbell, P. A., Balyeat, H. D., Cohen, E. A., Culbertson, W., Doughman, D. J., Fecko, P., McDonald, M. B., Smith, R. E., Wilson, L. B., and the PERK Study Group: Results of the prospective evaluation of radial keratotomy (PERK) study 4 years after surgery for myopia. JAMA 263:1083, 1990.
9. Lynn, M. J., Waring, G. O., Sperduto, R. D., and the PERK Study Group: Factors affecting outcome and predictability of radial keratotomy in the PERK study. Arch. Ophthalmol. 105:42, 1987.
10. Deitz, M. R., Sanders, D. R., and Raanan, M. G.: Progressive hyperopia in radial keratotomy. Ophthalmology 93:1284, 1986.
11. Arrowsmith, P. N., and Marks, R. G.: Visual, refractive and keratometric results of radial keratotomy. A five-year follow-up. Arch. Ophthalmol. 107:506, 1989.
12. Sawelson, H., and Marks, R. G.: Five-year results of radial keratotomy. Refract. Corneal Surg. 5:8, 1989.
13. Neumann, A. C., McCarty, G. R., Sanders, D. R., and Raanan, M. G.: Five-year refractive results of radial keratotomy. J. Cataract Refract. Surg. In press.
14. Deitz, M. R., Sanders, D. R., and Raanan, M. G.: A consecutive series (1982–1985) of radial keratotomies performed with the diamond blade. Am. J. Ophthalmol. 103:417, 1987.
15. Waring, G. O.: Another surprise from radial keratotomy. Refract. Corneal Surg. 5:6, 1989.
16. Waring, G. O., Moffitt, S. D., Gelender, H., Laibson, P. R., Lindstrom, R. L., Myers, W. D., Obstbaum, S. A., Rowsey, J. J., Safir, A., Schanzlin, A. J., Bourque, L. B., and the PERK Study Group: Rationale for and design of the National Eye Institute prospective evaluation of radial keratotomy (PERK) study. Ophthalmology 90:40, 1983.
17. Ferris, F. L., III, and Sperduto, R. D.: Standardized illumination for visual acuity testing in clinical research. Am. J. Ophthalmol. 94:97, 1982.

18. Ferris, F. L., III, Kassoff, A., Bresnick, G. H., and Bailey, I.: New visual acuity charts for clinical research. Am. J. Ophthalmol. 94:91, 1982.

19. Salz, J. J., Villasenor, R. A., Elander, R., Reader, A. L., and Swinger, C.: Four-incision radial keratotomy for low to moderate myopia. Ophthalmology 93:727, 1986.

20. Spigelman, A. V., Williams, P. A., and Lindstrom, R. L.: Further studies of four incision radial keratotomy. Refract. Corneal Surg. 5:292, 1989.

21. Deitz, M. R., Sanders, D. R., and Marks, R. G.: Radial keratotomy. An overview of the Kansas City study. Ophthalmology 91:467, 1984.

22. Schanzlin, D. J., Santos, V. R., Waring, G. O., Lynn, M. J., Bourque, L., Cantillo, N., Edwards, M., Justin, N., Reinig, J., and Roszka-Duggan, V.: Diurnal change in refraction, corneal curvature, visual acuity, and intraocular pressure after radial keratotomy in the PERK study. Ophthalmology 93:167, 1986.

23. Santos, V. R., Waring, G. O., Lynn, M. J., Schanzlin, D. J., Cantillo, N., Espinal, M., Garbus, J., Justin, N., and Roszka-Duggan, V.: Morning to evening change in refraction, corneal curvature, and visual acuity 2 to 4 years after radial keratotomy in the PERK study. Ophthalmology 95:1487, 1988.

24. MacCrae, S. M., Rich, L., Phillips, D., and Bedrossian, R.: Diurnal variation in vision after radial keratotomy. Am. J. Ophthalmol. 107:262, 1989.

25. Richmond, R. D.: Special report. Radial keratotomy as seen through operated eyes. J. Refract. Surg. 3:22, 1987.

26. Wyzinski, P., and O'Dell, L. W.: Diurnal cycle of refraction after radial keratotomy. Ophthalmology 94:120, 1987.

27. Brown, E. V. L.: Net average yearly changes in refraction of atropinized eyes from birth to beyond middle life. Arch. Ophthalmol. 19:719, 1938.

28. Nizam, A., Carter, J., Lynn, M. J., Waring, G. O., and the PERK Study Group: Changes in refractive error, keratometric power and best corrected visual acuity for unoperated myopic eyes in the prospective evaluation of radial keratotomy (PERK) study. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 30.

29. McDonnell, P. J., and Schanzlin, D. J.: Early changes in refractive error following radial keratotomy. Arch. Ophthalmol. 106:212, 1988.

30. Santos, V. R., Waring, G. O., Lynn, M. J., Holladay, J. T., Sperduto, R. D., and the PERK Study Group: Relationship between refractive error and visual acuity in the prospective evaluation of radial keratotomy (PERK) study. Arch. Ophthalmol. 105:86, 1987.

31. Parel, J. M., Simon, G., and Lowery, J. A.: The effect of hydration on central corneal curvature in laser and diamond knife keratotomy. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 479.

32. Binder, P. S., Nayak, S. K., Deg, J. K., Zavala, E. Y., and Sugar, J.: An ultrastructural and histochemical study of long-term wound healing after radial keratotomy. Am. J. Ophthalmol. 103:432, 1987.

33. Jester, J. V., Petroll, W. M., Feng, W., Sachdov, M., New, K., Essepian, J., and Cavanagh, H. D.: In vivo modulation of corneal curvature during wound healing in radial keratotomy. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 300.

34. Randa, M. R., Garana, W., Petroll, M., Feng, W., Cavanagh, H. D., and Jester, J. V.: Cell biology of corneal wound fibroblasts. Mechanism of wound contraction in radial keratotomy. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 3.

35. Richmond, R. D.: Radial keratotomy as seen through operated eyes. Part II. J. Refract. Surg. 4:91, 1988.

36. Busin, M., Suarez, H., Bieber, S., and McDonald, M. B.: Overcorrected visual acuity improved by antiglaucoma medication after radial keratotomy. Am. J. Ophthalmol. 101:374, 1985.

A Comparison of Penetrating Keratoplasty to Epikeratoplasty in the Surgical Management of Keratoconus

John D. Goosey, M.D., Thomas C. Prager, Ph.D., Claire B. Goosey, M.S., Eugene F. Bird, M.D., and James C. Sanderson, M.D.

Of 40 patients intolerant to contact lenses, 47 eyes with keratoconus were surgically corrected with either epikeratoplasty (N = 31) or penetrating keratoplasty (N = 16). The percentage of eyes in both groups that had visual acuity of 20/40 or better with contact lenses at one year were equal (14 of 15 eyes [93.3%] in the penetrating keratoplasty group; 27 of 29 eyes [93.1%] in the epikeratoplasty group); however, the penetrating keratoplasty procedure resulted in a higher percentage of eyes that had visual acuity of 20/20 than the epikeratoplasty group (11 of 15 eyes [73%] compared with seven of 29 eyes [24.1%], respectively). Both procedures resulted in significant corneal flattening, with the penetrating keratoplasty group producing an average of 3 diopters more keratometric reduction than the epikeratoplasty group one year postoperatively. Although no irreversible graft failures occurred, five of 16 eyes (31%) in the penetrating keratoplasty group had graft reactions. No serious complications were noted in the eyes of the epikeratoplasty group. Both procedures were effective in the surgical management of keratoconus.

PENETRATING KERATOPLASTY is a well-established surgical treatment for patients with keratoconus who are intolerant to contact lens wear.[1-3] Despite the excellent vision obtained with this procedure, a significant number of patients have postoperative complications secondary to immune reactions. Wilhelmus[4] summarized 25 articles with a combined total of 2,758 keratoconus procedures and found the incidence of rejection episodes after penetrating keratoplasty varied from 6% to 56% with a weighted average of 18%. Fortunately, most graft reactions can be treated successfully with corticosteroids and usually do not offset the excellent results obtained with penetrating keratoplasty. Nevertheless, long-term studies of penetrating keratoplasty have identified that a significant number of grafts ultimately fail (7% to 10%[5,6]) with endothelial rejection being the most common reason for graft failure.

To circumvent the problem of endothelial rejection, the use of lamellar keratoplasty has been advocated for the treatment of keratoconus. Lamellar keratoplasty, however, is generally considered a technically difficult procedure, which yields visual results inferior to penetrating keratoplasty.[7,8] When Kaufman and Werblin[9] introduced epikeratoplasty, an onlay form of lamellar keratoplasty, for the treatment of keratoconus, the procedure offered the safety advantages of lamellar keratoplasty and was relatively easy to perform.[9] Subsequent studies confirmed that epikeratoplasty can effectively rehabilitate eyes of patients with keratoconus who are intolerant to contact lens wear and have no central corneal scarring. The nationwide study of epikeratoplasty for keratoconus reported the results of 35 surgeons who performed a total of 82 procedures with 64 of the patients (78%) having 20/40 or better best-corrected visual acuity postoperatively.[10] Dietz and Durrie[11] described 19 procedures with 13 of 16 patients (81%) having 20/40 or better visual acuity six months after epikeratoplasty for keratoconus.

The introduction of epikeratoplasty as an effective alternative to penetrating keratoplasty has raised questions as to which surgical mo-

Accepted for publication Oct. 19, 1990.

From the Department of Ophthalmology, University of Texas Medical School, Houston, Texas. This study was supported in part by Lions Eye Bank, Houston, Texas, and The Rockwell Fund, Houston, Texas. Dr. John D. Goosey and Ms. Claire B. Goosey have a proprietary interest in Cryo-Optics.

Reprint requests to John D. Goosey, M.D., Hermann Eye Center, 6411 Fannin St., Houston, TX 77030.

dality is optimal for the treatment of keratoconus. We compared these two procedures directly. Two previous studies, each with small numbers of patients, have compared epikeratoplasty to penetrating keratoplasty.[12,13] We treated 47 patients with keratoconus who had undergone epikeratoplasty or penetrating keratoplasty.

Patients and Methods

Epikeratoplasty group—Since February 1986, 26 patients (31 eyes) underwent epikeratoplasty for keratoconus. All procedures were performed by one of us (J.D.G.) after obtaining informed consent from the patients. The criteria for inclusion in this surgical group were contact lens–intolerant keratoconus and no corneal scarring within 2.0 mm of the visual axis. The average age of the patients was 30 ± 9 years (range, 15 to 47 years). There were 16 females and ten males. Five patients underwent bilateral procedures, and one patient had the epigraft removed and replaced because of inadequate flattening of the recipient cornea. The average follow-up period was 19 ± 8.5 months (range, six to 36 months). In all cases, the lenticule was prepared without lyophilization. We initially processed human corneal tissue in a corneal press to restore the tissue to a uniform hydration state. The tissue was then frozen and lathed on a cryolathe to form a plano-power lenticule. The central thickness was 0.2 mm with a 1.5-mm wing and an overall diameter of 9.0 mm. The lenticule was stored in McCarey-Kaufman medium for a maximum of 72 hours before surgery.

The surgical technique consisted of mechanical epithelial débridement of the recipient cornea followed by trephination with an 8.0-mm single-blade vacuum trephine to a depth of approximately 0.25 mm. A 0.5-mm annular keratectomy was then performed on the inner aspect of the trephination. The lenticule was secured with 16 interrupted 10-0 nylon sutures with adjustable knots. The sutures were adjusted under a surgical astigmometer. Pressure patching was used postoperatively until the graft surface was completely epithelialized. Epithelialization was complete by the fourth postoperative day in all cases. Sutures were removed when spontaneous loosening occurred; selective suture removal for astigmatism control was initiated at the end of the second postoperative month. By the sixth postoperative month, all sutures had been removed.

Penetrating keratoplasty group—Since 1986, 14 patients (16 eyes) underwent penetrating keratoplasty for keratoconus by one of us (J.D.G.). All patients had significant corneal scarring over the visual axis, thereby excluding them as appropriate candidates for epikeratoplasty. The average age of the patients undergoing penetrating keratoplasty was 37 ± 11 years (range, 23 to 64 years). There were four women and ten men. Two patients underwent bilateral penetrating keratoplasty. The average follow-up period was 20 ± 12 months (range, six to 36 months).

The surgical technique in all 16 cases consisted of an 8.2-mm graft placed into an 8.0-mm recipient bed, which was prepared with vacuum trephine and corneal scissor dissection. The graft was secured to the recipient bed with 16 interrupted 10-0 nylon sutures in 12 cases and with eight interrupted sutures and a 16-bite 10-0 nylon running suture in four cases. All sutures were removed by one year postoperatively. Selective suture removal to correct astigmatism was initiated after the third postoperative month.

TABLE 1
POSTOPERATIVE UNCORRECTED VISUAL ACUITY AFTER PENETRATING KERATOPLASTY AND EPIKERATOPLASTY

	PENETRATING KERATOPLASTY GROUP					EPIKERATOPLASTY GROUP				
SNELLEN VISUAL ACUITY	3 MONTHS (N = 13) NO. (%)	6 MONTHS (N = 16) NO. (%)	12 MONTHS (N = 15) NO. (%)	24 MONTHS (N = 5) NO. (%)	36 MONTHS (N = 2) NO. (%)	3 MONTHS (N = 23) NO. (%)	6 MONTHS (N = 28) NO. (%)	12 MONTHS (N = 28) NO. (%)	24 MONTHS (N = 15) NO. (%)	36 MONTHS (N = 5) NO. (%)
20/10–20/20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
20/25–20/30	1 (8)	2 (12)	6 (40)	3 (60)	1 (50)	0 (0)	2 (7)	2 (7)	0 (0)	1 (20)
20/40	2 (15)	3 (19)	0 (0)	0 (0)	0 (0)	2 (9)	1 (4)	4 (14)	0 (0)	0 (0)
Worse than 20/50	10 (77)	11 (69)	9 (60)	2 (40)	1 (50)	20 (87)	25 (89)	22 (79)	15 (100)	4 (80)

TABLE 2
SPECTACLE-CORRECTED VISUAL ACUITY AFTER PENETRATING KERATOPLASTY AND EPIKERATOPLASTY

	PENETRATING KERATOPLASTY GROUP						EPIKERATOPLASTY GROUP					
SNELLEN VISUAL ACUITY	PREOP-ERATIVE (N = 16) NO. (%)	3 MONTHS (N = 12) NO. (%)	6 MONTHS (N = 16) NO. (%)	12 MONTHS (N = 15) NO. (%)	24 MONTHS (N = 6) NO. (%)	36 MONTHS (N = 2) NO. (%)	PREOP-ERATIVE (N = 31) NO. (%)	3 MONTHS (N = 23) NO. (%)	6 MONTHS (N = 28) NO. (%)	12 MONTHS (N = 29) NO. (%)	24 MONTHS (N = 15) NO. (%)	36 MONTHS (N = 6) NO. (%)
20/10–20/20	0 (0)	0 (0)	0 (0)	5 (33)	1 (17)	1 (50)	0 (0)	1 (4)	3 (11)	2 (7)	0 (0)	1 (17)
20/25–20/30	0 (0)	5 (42)	14 (88)	9 (60)	5 (83)	1 (50)	4 (13)	5 (22)	10 (36)	12 (41)	7 (46)	1 (17)
20/40	0 (0)	4 (33)	0 (0)	0 (0)	0 (0)	0 (0)	4 (13)	6 (26)	7 (25)	8 (28)	4 (27)	1 (17)
Worse than 20/50	16 (100)	3 (25)	2 (12)	1 (7)	0 (0)	0 (0)	23 (75)	11 (48)	8 (29)	7 (24)	4 (27)	3 (50)

Although the entry criteria for the two groups were different, the patient population was homogeneous with respect to age, contact lens intolerance, and presurgical corneal curvature (keratometry). At one year postoperatively, 13 of 14 patients (93%) returned for follow-up.

Results

To assess the relative effectiveness of epikeratoplasty and penetrating keratoplasty in the visual rehabilitation of keratoconus, data were analyzed regarding Snellen visual acuity (uncorrected, spectacle-corrected, and contact lens–corrected), spherical equivalents, and keratometry readings at three, six, 12, 24, and 36 months postoperatively.

In every category of comparison, penetrating keratoplasty produced superior visual acuity relative to epikeratoplasty. One year postoperatively, six of 28 eyes (21%) in the epikeratoplasty group had visual acuity of 20/40 or better without correction compared with six of 15 eyes (40%) in the penetrating keratoplasty group (Table 1).

Before the operation, only eight of 31 eyes (26%) in the epikeratoplasty group had spectacle-corrected visual acuity of 20/40 or better because of irregular astigmatism; all of the 16 eyes in the penetrating keratoplasty group had best-corrected spectacle visual acuity worse than 20/40 because of corneal scars in the visual axis. One year postoperatively, most of the patients in both groups demonstrated improved spectacle-corrected vision with 22 of 29 eyes (76%) in the epikeratoplasty group and 14 of 15 eyes (93%) in the penetrating keratoplasty group having 20/40 or better visual acuity (Table 2).

Best-corrected visual acuity was obtained with contact lenses (Table 3). Figure 1 compares the contact lens–corrected visual acuity of both groups one year postoperatively. Fourteen of 15 eyes (93%) in the penetrating keratoplasty group and 27 of 29 eyes (93%) in the epikeratoplasty group had contact lens–corrected visual acuity of 20/40 or better at one year postoperatively. However, with contact lens correction, 11 of 15 eyes (73%) in the penetrating keratoplasty group had visual acuity of 20/20 or better, whereas only seven of 29 eyes (24%) in the epikeratoplasty group had visual acuity of

TABLE 3
CONTACT LENS–CORRECTED VISUAL ACUITY AFTER PENETRATING KERATOPLASTY AND EPIKERATOPLASTY

	PENETRATING KERATOPLASTY GROUP						EPIKERATOPLASTY GROUP					
SNELLEN VISUAL ACUITY	PREOP-ERATIVE (N = 16) NO. (%)	3 MONTHS (N = 6) NO. (%)	6 MONTHS (N = 15) NO. (%)	12 MONTHS (N = 15) NO. (%)	24 MONTHS (N = 7) NO. (%)	36 MONTHS (N = 2) NO. (%)	PREOP-ERATIVE (N = 30) NO. (%)	3 MONTHS (N = 0) NO. (%)	6 MONTHS (N = 25) NO. (%)	12 MONTHS (N = 29) NO. (%)	24 MONTHS (N = 13) NO. (%)	36 MONTHS (N = 5) NO. (%)
20/10–20/20	0 (0)	2 (33)	4 (27)	11 (73)	3 (43)	2 (100)	1 (3)	0 (0)	5 (20)	7 (24)	3 (24)	1 (20)
20/25–20/30	0 (0)	4 (67)	9 (60)	3 (20)	3 (43)	0 (0)	12 (40)	0 (0)	10 (40)	14 (48)	7 (54)	3 (60)
20/40	0 (0)	0 (0)	1 (7)	0 (0)	1 (14)	0 (0)	8 (27)	0 (0)	7 (28)	6 (21)	2 (15)	1 (20)
Worse than 20/50	16 (100)	0 (0)	1 (7)	1 (7)	0 (0)	0 (0)	9 (30)	0 (0)	3 (12)	2 (7)	1 (8)	0 (0)

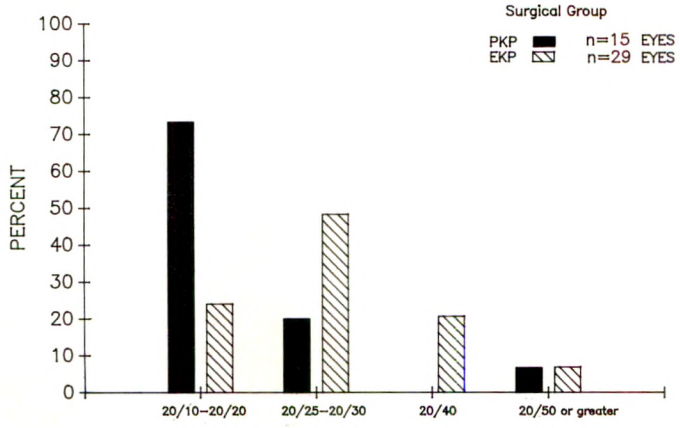


Fig. 1 (Goosey and associates). A comparison of best-corrected visual acuity for penetrating keratoplasty and epikeratoplasty one year postoperatively. The percentages of eyes that fall within four visual acuity categories are depicted. (PKP indicates penetrating keratoplasty and EKP indicates epikeratoplasty.)

20/20 or better after one year, which represents a significant difference in frequency (chi-square = 48.06, $P < .0001$). Multiple linear regression analysis on contact lens–corrected visual acuity by surgical group did not demonstrate a significant change in slope from six to 36 months for either group (epikeratoplasty, $r = -.14$, $F = 1.45$, $P = .23$; penetrating keratoplasty, $r = -.17$, $F = 0.98$, $P = .33$). These results suggest stability of results over time for both surgical groups (Fig. 2). A small but significant difference in contact lens–corrected visual acuity between groups over time was noted (multiple linear regression analysis between groups, $F = 3.5$, $P = .03$). This difference reflects a slightly better visual rehabilitation outcome with the penetrating keratoplasty procedure.

Patients in both groups had similar preoperative keratometry readings. The average keratometry reading for 31 eyes in the epikeratoplasty group was 60.10 diopters (standard deviation, 9.84 diopters) and the average astigmatism was 9.86 diopters (standard deviation, 8.17 diopters). The 14 eyes in the penetrating keratoplasty group had an average keratometry reading of 58.03 diopters (standard deviation, 7.38 diopters) and demonstrated an average astigmatism of 10.23 diopters (standard deviation, 10.08 diopters) (Table 4). Both procedures resulted in significant corneal flattening with the eyes in the penetrating keratoplasty group having an average of 3 diopters more flattening than the eyes in the epikeratoplasty group one year postoperatively (Fig. 3). The keratometry measurements between six and 36 months for each group do not show a significant trend toward preoperative keratometry values (epikeratoplasty, $r = .12$, $F = 0.96$, $P = .33$; penetrating keratoplasty, $r = .21$, $F = 1.33$, $P = .26$). Although both procedures produced substantial keratometric reductions, there was a highly significant difference between groups, which reflected the greater amount of corneal flattening found in eyes in the penetrating keratoplasty group ($F = 32.56$, $P < .00001$).

Table 5 summarizes the mean and standard deviation of spherical equivalent and range for

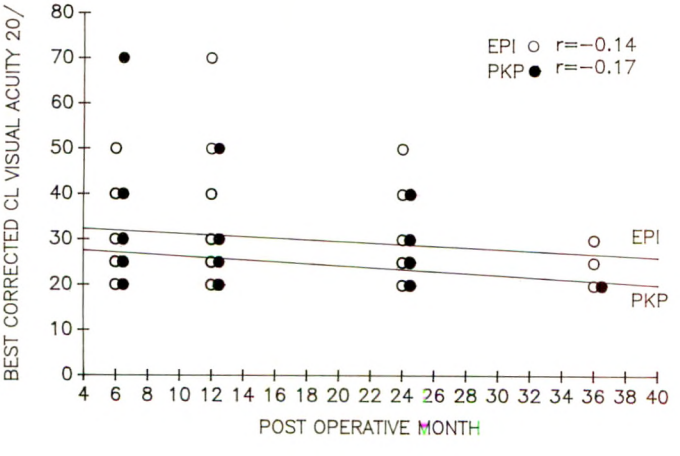


Fig. 2 (Goosey and associates). Scattergram of contact lens–corrected visual acuity over postoperative months for both penetrating keratoplasty and epikeratoplasty groups. Lines of best fit have been drawn through the individual data points of each group. (EPI indicates epikeratoplasty and PKP indicates penetrating keratoplasty.)

TABLE 4
KERATOMETRY SUMMARY AFTER PENETRATING KERATOPLASTY AND EPIKERATOPLASTY

	PENETRATING KERATOPLASTY GROUP					EPIKERATOPLASTY GROUP				
	PREOP-ERATIVE (N = 14)	6 MONTHS (N = 12)	12 MONTHS (N = 11)	24 MONTHS (N = 8)	36 MONTHS (N = 3)	PREOP-ERATIVE (N = 31)	6 MONTHS (N = 26)	12 MONTHS (N = 29)	24 MONTHS (N = 13)	36 MONTHS (N = 2)
Grand mean	58.03,±7.4	42.85,±3.5	43.71,±3.7	44.43,±1.9	44.54,±2.5	60.10,±9.8	48.43,±3.0	48.87,±2.9	49.01,±3.0	48.72,±0.1
High K	63.14,±8.8	44.25,±3.3	45.20,±3.7	46.00,±2.1	46.04,±2.6	65.22,±12.3	50.18,±3.3	50.42,±3.3	51.22,±3.7	50.44,±0.8
Low K	52.91,±9.0	41.46,±4.0	42.21,±3.9	42.87,±2.2	43.04,±2.6	54.98,±8.4	46.68,±3.0	47.32,±2.9	46.81,±2.8	47.00,±0.7
Delta K	10.23,±10.0	2.79,±12.1	2.99,±1.8	3.13,±2.0	3.00,±1.1	10.24,±7.7	3.50,±2.2	3.10,±1.9	4.41,±2.6	3.44,±1.5

each group preoperatively and at six and 12 months postoperatively. Because of the irregular astigmatism characteristically found in keratoconus, manifest preoperative correction may vary greatly from one visit to the next for an individual patient and has limited clinical value. One year postoperatively, however, the eyes in both groups demonstrated a 40% to 50% reduction from preoperative myopia.

Of 32 epikeratoplasty procedures, one (3%) resulted in inadequate flattening of the recipient cornea, necessitating removal and replacement of the epigraft. Final contact lens–corrected visual acuity of 20/30 was attained in this patient one year after the second operation. No persistent epithelial defects occurred with any of the epikeratoplasty grafts in this series.

In the penetrating keratoplasty group, graft reactions were observed in five of 16 eyes (31%) during the first postoperative year, and a second graft reaction occurred in one patient during the second year. All immune reactions were successfully treated with topical corticosteroids. One patient had a traumatic wound dehiscence at four months postoperatively that was successfully repaired, with final best-corrected visual acuity of 20/20.

Discussion

In this study 41 of 44 eyes (93%) of both surgical groups had best-corrected visual acuity of 20/40 or better one year postoperatively. This confirms the findings of other reports[12,13] in which the two procedures yielded equivalent 20/40 or better best-corrected visual acuity. In contrast to these studies, we extended the analysis to include visual acuity better than 20/40. Despite clear grafts in both groups, the penetrating keratoplasty procedure resulted in a significantly higher percentage of eyes that had visual acuity of 20/20 than that found in the epikeratoplasty group (Fig. 1). To explain this discrepancy, we postulate that the flattening of the recipient cornea associated with the epikeratoplasty procedure results in the formation of microscopic folds in the recipient Bowman's layer, which occasionally give the interface a

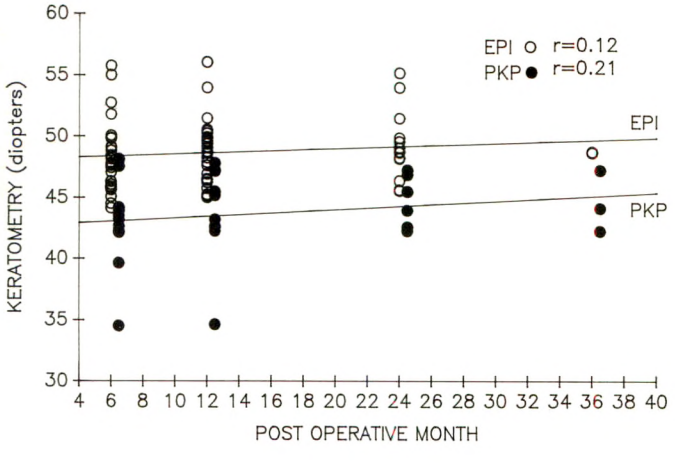


Fig. 3 (Goosey and associates). Scattergram of average keratometry measurements over postoperative months for both penetrating keratoplasty and epikeratoplasty groups. Lines of best fit have been drawn through the individual data points of each group. (EPI indicates epikeratoplasty and PKP indicates penetrating keratoplasty.)

TABLE 5
SPHERICAL EQUIVALENT IN DIOPTERS AFTER PENETRATING KERATOPLASTY AND EPIKERATOPLASTY

	PENETRATING KERATOPLASTY GROUP						EPIKERATOPLASTY GROUP					
	PREOP-ERATIVE (N = 8)	3 MONTHS (N = 12)	6 MONTHS (N = 15)	12 MONTHS (N = 15)	24 MONTHS (N = 8)	36 MONTHS (N = 4)	PREOP-ERATIVE (N = 30)	3 MONTHS (N = 20)	6 MONTHS (N = 28)	12 MONTHS (N = 28)	24 MONTHS (N = 24)	36 MONTHS (N = 6)
Average	−3.41	−1.83	−1.94	−1.93	−2.53	−0.41	−7.91	−2.12	−3.28	−3.83	−7.35	−5.06
Standard deviation	4.0	4.5	3.2	4.1	2.5	2.8	7.3	3.6	3.5	2.8	4.3	3.2
Low range	−10.0	−7.75	−7.63	−9.00	−6.13	−4.0	−35.75	−8.60	−9.50	−11.63	−20.00	−8.88
High range	1.0	4.63	3.63	5.13	0.63	2.88	1.38	3.00	1.50	1.13	−3.5	−0.75

granular appearance when examined with biomicroscopy. These interface changes may produce a loss of retinal image contrast secondary to increased glare.[14] Our results indicate that patients who underwent penetrating keratoplasty had a better chance of attaining 20/20 best-corrected visual acuity. This should be considered when determining the optimal procedure for a given patient.

Both surgical procedures resulted in significant and stable corneal flattening as determined by sequential keratometry readings. This caused a reduction in preoperative myopia for both surgical groups (Table 5). Flattening was greatest in the eyes in the penetrating keratoplasty group, although both groups of patients were successfully fitted with contact lenses. Steeper postoperative corneas, found in epikeratoplasty patients, usually required a small diameter (7.7-mm to 7.8-mm), gas-permeable contact lens that was designed to fit within the boundaries of the graft.

Epikeratoplasty for the correction of keratoconus is generally considered safer than penetrating keratoplasty because it is an extraocular procedure that maintains the structural integrity of the globe and minimizes the risk of immune reaction. The final visual outcome, however, is often superior with penetrating keratoplasty. Unfortunately there is no simple answer as to which procedure is optimal for the individual patient who is intolerant to contact lens wear and has no central scarring. Appraisal of a patient's lifestyle and self-care capability are helpful in determining which surgical procedure should be performed. Epikeratoplasty might be the preferred procedure for patients who engage in strenuous physical activity, because the partial-thickness incision created during this procedure is more structurally sound than the full-thickness incision produced during penetrating keratoplasty procedures. Compliance with postoperative instructions and access to ophthalmic care are important for both procedures in the early postoperative period but become less important after suture removal for the patient who has undergone epikeratoplasty, since the risk of immune reaction is negligible. Alternatively, graft failure secondary to immune reaction is a lifelong threat to vision for patients who have undergone penetrating keratoplasty. In our study, five of the 16 eyes (31%) that underwent penetrating keratoplasty had graft reactions. Although each graft reaction was successfully treated, their occurrence underscores the importance for patients who have undergone penetrating keratoplasty to have access to ophthalmic care.

This study confirms and expands previous comparisons between epikeratoplasty and penetrating keratoplasty procedures. Our analysis has attempted to clarify the role of each surgical alternative in the management of keratoconus. We believe that epikeratoplasty is not a replacement for penetrating keratoplasty but should be considered an effective modality for the treatment of appropriately selected patients with keratoconus.

References

1. Paton, R. T.: Corneal transplantation. A review of 365 operations. Arch. Ophthalmol. 52:871, 1954.

2. Anseth, A.: Keratoplasty for keratoconus. A report of 50 operated eyes. Acta Ophthalmol. 45:684, 1967.

3. Payne, J. W.: Primary penetrating keratoplasty for keratoconus. A long-term follow-up. Cornea 1:21, 1982.

4. Wilhelmus, K. R.: In discussion: Epstein, R. J.,

Seedor, J. A., Dreizen, N. G., Stulting, R. A., Waring, G. O., III, Wilson, L. A., and Cavanagh, H. D.: Penetrating keratoplasty for herpes simplex keratitis and keratoconus. Allograft rejection and survival. Ophthalmology 94:943, 1987.

5. Epstein, R. J., Seedor, J. A., Dreizen, N. G., Stulting, R. D., Waring, G. O., III, Wilson, L. A., and Cavanagh, H. D.: Penetrating keratoplasty for herpes simplex keratitis and keratoconus. Allograft rejection and survival. Ophthalmology 94:935, 1987.

6. Paglen, P. G., Fine, M., Abbott, R. L., and Webster, R. G.: The prognosis for keratoplasty in keratoconus. Ophthalmology 89:651, 1982.

7. Wood, T. O.: Lamellar transplants in keratoconus. Am. J. Ophthalmol. 83:543, 1977.

8. Richard, J. M., Paton, D., and Gasset, A. R.: A comparison of penetrating keratoplasty and lamellar keratoplasty in the surgical management of keratoconus. Am. J. Ophthalmol. 86:807, 1978.

9. Kaufman, H. E., and Werblin, T. P.: Epikeratophakia for the treatment of keratoconus. Am. J. Ophthalmol. 93:342, 1982.

10. McDonald, M. B., Kaufman, H. E., Durrie, D. S., Keates, R. H., and Sanders, D. R.: Epikeratophakia for keratoconus. The Nationwide study. Arch. Ophthalmol. 104:1294, 1986.

11. Dietz, T. R., and Durrie, D. S.: Indications and treatment of keratoconus using epikeratophakia. Ophthalmology 95:236, 1988.

12. McDonald, M. B., Safir, A., Waring, G. O., III, Schlichtemeier, W. R., Kissling, G. E., and Kaufman, H. E.: A preliminary comparative study of epikeratophakia or penetrating keratoplasty for keratoconus. Am. J. Ophthalmol. 103:467, 1987.

13. Steinert, R. F., and Wagoner, M. D.: Long-term comparison of epikeratoplasty and penetrating keratoplasty for keratoconus. Arch. Ophthalmol. 106:493, 1988.

14. Prager, T. C.: Glare testing. Basic concepts and identification of sources of methodological error when evaluating instruments. In Nadler, M. P., Nadler, D. J., and Miller, D. (eds.): Glare and Contrast Sensitivity for Clinicians. New York, Springer-Verlag, 1990, pp. 33–43.

OPHTHALMIC MINIATURE

Zelke would turn her eyes on him slowly—they moved around into sight from under her eyebrows like the barrel of a well-kept gun; they were hard like metal and strong, and she was always conscious of them even in sleep. When she would close her eyes before saying her prayers, she would remark to Swart, "I draw the hood over the artillery." And Swart would smile, nodding his large head.

Djuna Barnes, *Smoke*, in *The Heath Anthology of American Literature*, vol. 2
D. C. Heath and Co., 1990, p. 1260

Endoscopic Laser-Assisted Lacrimal Surgery

Russell S. Gonnering, M.D., David B. Lyon, M.D., and John C. Fisher, Sc.D.

Since Sept. 1, 1989, we have successfully performed 20 video-endoscopic, transnasal, laser-assisted lacrimal procedures on 18 patients ranging in age from 3 to 88 years. This technique avoided a cutaneous scar and caused less surgical trauma and bleeding than that seen in conventional lacrimal surgery, which shortened postoperative recovery time and lessened postoperative pain. With minor modifications in surgical technique, both dacryocystorhinostomy and conjunctivodacryocystorhinostomy were performed with either the potassium titanyl phosphate or carbon dioxide lasers. The use of the video endoscope allowed laser surgery to be performed across a broad range of intranasal structural variations and provided an excellent medium for teaching this new technique.

SINCE THE DESCRIPTION of external dacryocystorhinostomy by Toti[1] in 1904, subsequent modifications by Dupuy-Dutemp and Bourguet[2,3] in 1920 and 1921, and conjunctivodacryocystorhinostomy with tube placement by Jones[4] in 1962, these two surgical procedures have provided the mainstay of therapy for patients with obstruction of the lacrimal excretory system. Both procedures involve an external approach to the lacrimal system with attendant surgical trauma to surrounding structures to gain the necessary exposure to perform the bypass of the lacrimal system.

Massaro, Gonnering, and Harris[5] described endonasal laser dacryocystorhinostomy using a high-energy argon laser and the operating microscope. We modified this technique, employed video endoscopy, and used either the carbon dioxide or potassium titanyl phosphate laser to perform both dacryocystorhinostomy and conjunctivodacryocystorhinostomy.

Accepted for publication Oct. 10, 1990.

From the Department of Ophthalmology, University of Wisconsin, Madison, Wisconsin (Drs. Gonnering and Lyon); and St. Luke's Medical Center, Milwaukee, Wisconsin (Drs. Gonnering, Lyon, and Fisher).

Reprint requests to Russell S. Gonnering, M.D., Ste. 950, 2600 N. Mayfair Rd., Milwaukee, WI 53226.

Patients and Methods

Since Sept. 1, 1989, we have performed 20 endoscopic laser-assisted lacrimal procedures on 18 patients. Data concerning these patients are found in the Table. The age range of these patients at the time of surgery was 3 to 88 years. The surgery was performed in an outpatient setting with local anesthesia and intravenous sedation, unless the patient's age or strong personal preferences necessitated general anesthesia. Patients were excluded if there was suspicion of a lacrimal sac neoplasm or if there was evidence of severe posttraumatic bony deformity of the lacrimal sac fossa.

The patients were given two sprays of 0.05% oxymetazoline hydrochloride nasal spray in the affected nostril to begin shrinkage of the nasal mucosa. After adequate intravenous sedation or introduction of general anesthesia, 4% topical cocaine was applied on pledgets to the anteronasal passages. Anesthesia of the medial commissure and lacrimal sac fossa was obtained by local anesthetic injection techniques.

After at least seven minutes, the cocaine packing was removed and a 0-degree operating rod telescope with attached videocamera was introduced into the nose. Examination of the area anterior to middle nasal turbinate was then performed.

For dacryocystorhinostomy, a modified 20-gauge fiberoptic light pipe was lubricated with antibiotic ointment, inserted through the dilated inferior or superior canaliculus, and advanced into the lacrimal sac into contact with the medial wall of the lacrimal sac fossa. The light pipe was held in position with sterile tape.

For conjunctivodacryocystorhinostomy, a partial carunculectomy was performed if needed. Next, the 16-gauge × 2½-inch long radiopaque catheter over a 20-gauge introducer needle was directed from the caruncle, into the lacrimal sac fossa, and up to the lacrimal bone

TABLE
DATA ON PATIENTS UNDERGOING LASER-ASSISTED LACRIMAL SURGERY*

CASE NO., AGE (YRS), SEX	PROCEDURE	LASER	FOLLOW-UP (MOS)	
			FROM SURGERY	FROM TUBE REMOVAL
1, 66, F	Dacryocystorhinostomy	Carbon dioxide	13	7
2, 88, F	Dacryocystorhinostomy	Carbon dioxide	13	7
3, 50, F	Conjunctivodacryocystorhinostomy	Carbon dioxide	12	NA
4, 49, M	Dacryocystorhinostomy	Carbon dioxide	12	6
5, 59, M	Conjunctivodacryocystorhinostomy	Carbon dioxide	11	NA
6, 29, F	Conjunctivodacryocystorhinostomy (2)	Potassium titanyl phosphate	6	NA
7, 80, F	Conjunctivodacryocystorhinostomy	Potassium titanyl phosphate	6	NA
8, 33, M	Dacryocystorhinostomy	Potassium titanyl phosphate	6	2
9, 75, F	Dacryocystorhinostomy	Potassium titanyl phosphate	6	1.5
10, 82, F	Bilateral dacryocystorhinostomy	Potassium titanyl phosphate	4	0
11, 32, F	Dacryocystorhinostomy	Potassium titanyl phosphate	4	0
12, 59, F	Dacryocystorhinostomy	Potassium titanyl phosphate	4	Tube in place
13, 76, F	Dacryocystorhinostomy	Potassium titanyl phosphate	4	Tube in place
14, 68, F	Dacryocystorhinostomy	Potassium titanyl phosphate	3	Tube in place
15, 3, M	Dacryocystorhinostomy	Potassium titanyl phosphate	3	Tube in place
16, 46, F	Dacryocystorhinostomy	Potassium titanyl phosphate	2.5	Tube in place
17, 22, M	Dacryocystorhinostomy	Potassium titanyl phosphate	2.5	Tube in place
18, 77, F	Dacryocystorhinostomy	Potassium titanyl phosphate	2	Tube in place

*NA indicates not applicable.

(Fig. 1). The needle was removed, and the catheter hub was cut off with scissors to allow passage of the light pipe through the catheter tip up to the lacrimal bone.

With the endoscope, a discrete spot of transilluminated light from the light pipe could be seen, which marked the site of intended rhinostomy (Fig. 2). To visualize this spot, the light from the endoscope was reduced to its lowest setting. If a diffuse spot indicated lack of contact between the light pipe and the lacrimal bone, repositioning of the light pipe was necessary. Local anesthetic with 1:100,000 epinephrine was then injected under endoscopic control into the nasal mucosa overlying the spot. If viewing of this area was awkward with the 0-degree telescope, a better view was possible by substituting the 30-degree telescope.

Because of the potential for ocular damage, especially with visible light lasers, appropriate laser safety precautions for the patient and the operating team were taken. The patient's eyes were covered with a doubled strip of aluminum foil, reflective side out, taped in place, and further covered with a moistened sponge. All members of the operating team wore appropriately filtered protective glasses. If oxygen was administered to an awake patient, it was stopped during laser administration to prevent the danger of flash fire in the operative field. If general anesthesia was used, the endotracheal tube was protected with aluminum foil.

Laser rhinostomy was then performed with video-endoscopic visualization. With the potassium titanyl phosphate laser, the energy was delivered through a 300- to 600-μm fiber that was passed through an angulated endoscopic laser suction tip. An electronically activated filter was fitted between the endoscope and the videocamera to prevent damage to the camera and allow visualization during the intense green light of laser delivery. Half-second pulses of 5 to 7 W of laser energy separated by half-second pauses were delivered in a noncontact mode to the mucosa surrounding the proposed rhinostomy. Next, in a near-contact mode, vaporization of tissue was performed to produce a 5- to 6-mm rhinostomy over the area of the light pipe for dacryocystorhinostomy and a 3- to 4-mm rhinostomy for conjunctivodacryocystorhinostomy.

The carbon dioxide laser energy was delivered through an articulated arm of a 55-W surgical laser attached to a small-wave guide. Distal mirrors of varying angulation on the wave guide directed both the helium-neon aim-

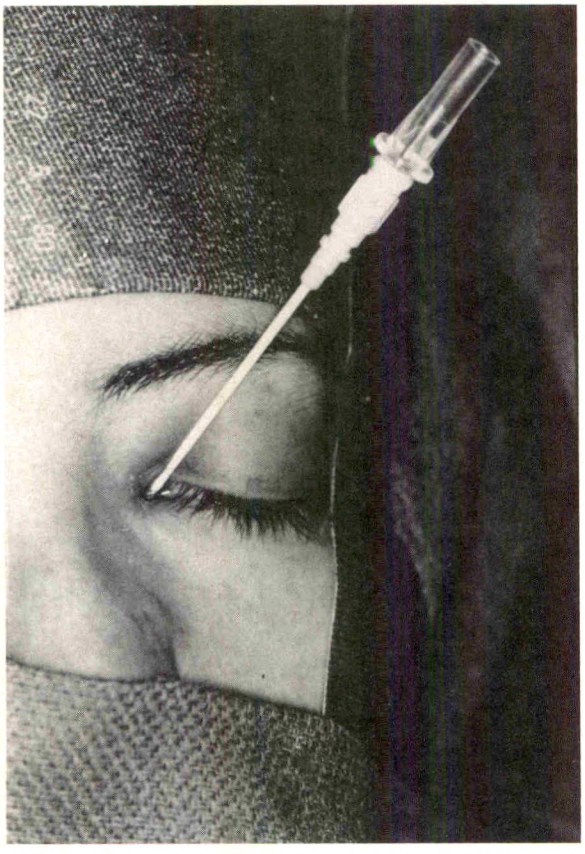


Fig. 1 (Gonnering, Lyon, and Fisher). Placement of introducer needle and catheter from caruncle across lacrimal sac fossa to abut the lacrimal bone.

ing beam and the carbon dioxide surgical beam to the desired area. The superpulse mode was used with 750 laser pulses per second delivering 8 to 14 W of energy to create rhinostomies similar to those produced with the potassium titanyl phosphate laser. With both lasers, the rhinostomy was produced in approximately three to five minutes of intermittent laser time with manipulation of the laser delivery beam and light pipe to create an opening of the desired size.

With dacryocystorhinostomy, after production of the rhinostomy, silicone intubation was performed and left in place for four to six months. With conjunctivodacryocystorhinostomy, after production of the rhinostomy, the light pipe was removed, the catheter was advanced into the nose, and the 0.035-inch flexible guide wire was inserted through the catheter, across the rhinostomy, and out the nostril (Fig. 3). The catheter was then viewed endoscopically, and an approximation of the proper Jones tube length was gauged by grasping the

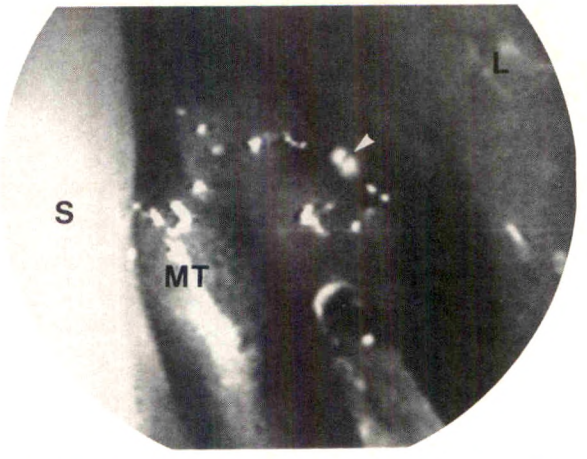


Fig. 2 (Gonnering, Lyon, and Fisher). Video-endoscopic view of left nasal passage during laser-assisted lacrimal surgery. (S, nasal septum; L, lateral nasal wall; MT, middle turbinate; arrowhead, discrete transillumination from light pipe.)

catheter with forceps at the medial commissure. The catheter was then withdrawn, leaving the guide wire in place. By measuring from the tip of the catheter to the forceps, an approximation of the length of Jones tube required can be made.

The vessel dilator was then cut approximately 4 cm from its distal end. This cut segment of dilator was threaded over the guide wire to act as an introducer for the Jones tube. The Jones tube was threaded on the guide wire behind the dilator segment (Fig. 4). With the vessel dilator ahead of it, the Jones tube was then easily advanced along the guide wire and into the nose. After proper Jones tube length was confirmed, the vessel dilator and guide wire were both removed from the nostril, and a suture was used to fix the Jones tube at the medial commissure for the initial postoperative healing phase.

Bleeding was usually minimal, and no packing was required unless there was an extensive turbinectomy. Postoperative medications included topical antibiotics and intranasal flunisolide 0.025% spray.

Results

Of the 20 procedures, five were conjunctivodacryocystorhinostomies. Five procedures were performed with the carbon dioxide laser, and 15 were performed with the potassium titanyl phosphate laser. The patient in Case 10

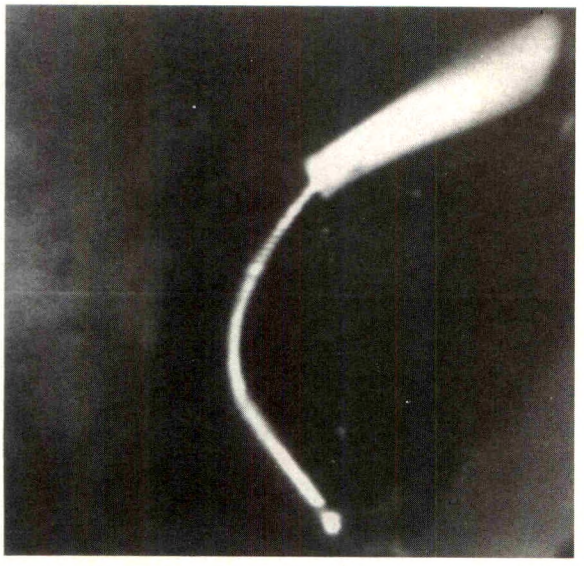


Fig. 3 (Gonnering, Lyon, and Fisher). Video-endoscopic view of passage of guide wire through catheter and into nose.



Fig. 4 (Gonnering, Lyon, and Fisher). Use of vessel dilator for placement of Jones tube along guide wire.

underwent bilateral dacryocystorhinostomy. The Jones tube in one patient (Case 6) dislodged one week postoperatively because she was rubbing her eye. Three weeks later, repeat conjunctivodacryocystorhinostomy was necessary in this patient since the rhinostomy had closed. Silicone tubing was removed from patients who had had dacryocystorhinostomy four to six months postoperatively. All patients had relief of symptoms with normal results of dye-disappearance tests.

Discussion

Caldwell[6] described the intranasal approach to dacryocystorhinostomy in 1893, in which a portion of the inferior turbinate was removed and the nasolacrimal canal was followed to the lacrimal sac. West[7] subsequently refined this technique by substituting a window resection over the lacrimal sac for wide resection. Although this method was used extensively earlier in this century, it has been all but abandoned by ophthalmologists, despite an increase in interest in the otolaryngologic literature.[8-11]

Within the past five years, a marked shift to endoscopic nasal and sinus surgery has occurred in otolaryngology.[12,13] The increased visualization allowed with this instrumentation has resulted in precise, microinvasive surgical technique, applicable to most patients, with high success and less morbidity than that seen with either open procedures or transnasal procedures done without the endoscope.

The endoscope has been used before in lacrimal surgery to document the patency of the rhinostomy,[14] as well as to manage failed dacryocystorhinostomy surgery[15] and complications of conjunctivodacryocystorhinostomy.[16] Four patients have been described by Rice[11] in whom conventional intranasal dacryocystorhinostomy was performed with the endoscope. Although endonasal lacrimal surgery can be performed with the operating microscope, the endoscope allows such procedures to be performed without the need for an open line of sight to the area of rhinostomy. Small movements of the patient do not require complex repositioning of the patient/microscope axis. The addition of the videocamera provides a magnified, on-screen view of the procedure to the surgeon and operating team, which is most useful when the surgical training of residents

and fellows is a secondary goal of the procedure.

Although endonasal dacryocystorhinostomy was originally described with the argon laser, both dacryocystorhinostomy and conjunctivodacryocystorhinostomy can be performed with either the potassium titanyl phosphate or the carbon dioxide laser. Both of these lasers currently are approved for intranasal surgery. The potassium titanyl phosphate laser consists of an Nd:YAG laser source, which is passed through a frequency-doubling crystal of potassium titanyl phosphate, producing a single output wavelength of 532.0 nm.[17,18] When used with a quartz delivery fiber, hemostasis is produced in the noncontact mode, and tissue vaporization can be accomplished with near-contact delivery. When used in the contact mode, precise tissue cutting is possible. Although the output of the argon laser is similar at 488.0 and 514.5 nm, direct contact of the fiber with tissue can result in fiber damage and the need to cleave the fiber to deliver precontact energy levels.

The carbon dioxide laser has had a history of successful use in the upper airway.[19,20] This infrared laser, at 10,600 nm, affords excellent vaporization of tissue with little thermal spread, especially when used in the superpulse mode. This wavelength, however, possesses only moderate hemostatic abilities and cannot as yet be transmitted effectively through a fiber. It must be internally reflected or focused from an articulated delivery arm down a waveguide, which must be flushed with an inert gas such as carbon dioxide to keep the distal reflective mirror free from char from the laser plume. We found this more complicated delivery system, though effective, to be somewhat more awkward to use than the quartz delivery fiber of the potassium titanyl phosphate laser.

Our guide wire and vessel dilator combination has been described in the percutaneous removal of dacryoliths in the syndrome of noninfectious dacryocystic retention.[21] The use of this combination in placement of Jones tubes significantly reduces the intraoperative frustration often accompanying attempts to pass the Jones tube with conventional techniques.[4] Other authors have emphasized that the surgical trauma and asymmetric reduction in the size of the rhinostomy in the healing phase of conjunctivodacryocystorhinostomy, as well as hypermobility of a tube in a large surgical rhinostomy, may contribute to postoperative tube malposition.[22-24] In our technique, the tube is already relatively snug in the rhinostomy at the conclusion of surgery, and minimal postoperative displacement, despite the early extrusion seen in one of our patients, should be expected. A valid comparison in rates of postoperative extrusion will require several years of observation.

Physicians must now evaluate not only the safety, but the cost and effectiveness of new technology and whether that new technology results in tangible benefits to the patient and society.[25,26] We believe that endoscopic laser-assisted lacrimal surgery is a new technology with significant individual and societal benefits for the following reasons: a cutaneous scar is avoided; surgical trauma is limited with less bleeding and postoperative pain; virtually all patients are treated as outpatients with most procedures performed under local anesthesia; postoperative recovery is shortened with most patients able to resume normal activities the next day.

The equipment used, though expensive, is shared by many surgical services in a hospital. Adaptation for lacrimal surgery allows increased utilization of this equipment and thus increases its cost-effectiveness. At our hospital, the use of the laser adds approximately $300 to the operative costs of lacrimal surgery. We believe this cost is more than balanced by the ability to perform all our lacrimal surgery on an outpatient basis and the much more rapid return of the patient to work, school, or other normal activities.

Contraindications to this technique include suspicion of lacrimal sac malignancy and severe bony deformity of the lacrimal sac fossa, which prevent accurate transillumination through the lacrimal bone. Because the anterior lacrimal crest is not removed with this technique, rhinostomy sites tend to be more inferior and posterior than those performed in conventional external approaches. Consequently, many patients require at least a partial turbinectomy, especially when conjunctivodacryocystorhinostomy is performed.[27] Although turbinate mucosa can safely be excised with the laser, care must be used when resecting conchal bone with the laser to avoid overheating and possible necrosis and sequestration.[20] Longer Jones tubes are often necessary, with most patients requiring a tube approximately 20 to 22 mm in length. Adequate supplies of long tubes must be available for this procedure.

Although the learning curve for video endoscopy is somewhat steep, the outcomes to date have been uniformly positive. The increased

experience of multiple surgeons, however, will be necessary to evaluate the clinical usefulness of these procedures adequately.

References

1. Toti, A.: Nuovo metodo conservatore di cura radicale delle suppurazioni croniche del sacco lacrimale (dacriocistorhinostomia). Clin. Moderna (Firenza) 10:385, 1904.
2. Dupuy-Dutemp, L., and Bourguet, M.: Note preliminaire sur en procede de dacryocystorhinostomie. Ann. Ocul. 157:445, 1920.
3. ———: Procede plastique de dacryocystorhinostomie et ses resultats. Ann. Ocul. 158:241, 1921.
4. Jones, L. T.: The cure of epiphora due to canalicular disorders, trauma and surgical failures on the lacrimal passages. Trans. Am. Acad. Ophthalmol. Otolaryngol. 66:506, 1962.
5. Massaro, B. M., Gonnering, R. S., and Harris, G. J.: Endonasal laser dacryocystorhinostomy. A new approach to nasolacrimal duct obstruction. Arch. Ophthalmol. 108:1172, 1990.
6. Caldwell, G. W.: Two new operations for obstruction of the nasal duct with preservation of the canaliculi and an incidental description of a new lachrymal probe. N. Y. Med. J. 57:581, 1893.
7. West, J. M.: A window resection of the nasal duct in cases of stenosis. Trans. Am. Ophthalmol. Soc. 12:654, 1914.
8. Jokinen, K., and Karjä, J.: Endonasal dacryocystorhinostomy. Arch. Otolaryngol. Head Neck Surg. 100:41, 1974.
9. Steadman, G. M.: Transnasal dacryocystorhinostomy. Otolaryngol. Clin. North Am. 18:107, 1985.
10. Rice, D. H.: Endoscopic intranasal dacryocystorhinostomy. A cadaver study. Am. J. Rhinol. 2:127, 1988.
11. ———: Endoscopic intranasal dacryocystorhinostomy results in four patients. Arch. Otolaryngol. Head Neck Surg. 116:1061, 1990.
12. Stammberger, H.: Endoscopic endonasal surgery. Concepts in treatment of recurring rhinosinusitis. Part I. Anatomic and pathophysiologic considerations. Otolaryngol. Head Neck Surg. 94:143, 1986.
13. Stammberger, H.: Endoscopic endonasal surgery. Concepts in treatment of recurring rhinosinusitis. Part II. Surgical technique. Otolaryngol. Head Neck Surg. 94:147, 1986.
14. Linberg, J. V., Anderson, R. L., Bumsted, R. M., and Barreres, R.: Study of intranasal ostium in external dacryocystorhinostomy. Arch. Ophthalmol. 100:1758, 1982.
15. Orcutt, J. C., Hillel, A., and Weymuller, E. A.: Endoscopic repair of failed dacryocystorhinostomy. Ophthalmol. Plast. Reconstr. Surg. 6:197, 1990.
16. Bartley, G. B., and Gustafson, R. O.: Complications of malpositioned Jones tubes. Am. J. Ophthalmol. 109:66, 1990.
17. Levine, H. L.: Endoscopy and the KTP/532 laser for nasal sinus disease. Ann. Otol. Rhinol. Laryngol. 98:46, 1989.
18. ———: Lasers and endoscopic rhinologic surgery. Otolaryngol. Clin. North Am. 22:739, 1989.
19. Selkin, S. G.: Pitfalls in intranasal laser surgery and how to avoid them. Arch. Otolaryngol. Head Neck Surg. 112:285, 1986.
20. ———: Laser turbinectomy as an adjunct to rhinoseptoplasty. Arch Otolaryngol. Head Neck Surg. 111:446, 1985.
21. Gonnering, R. S., and Bosniak, S. L.: Recognition and management of acute noninfectious dacryocystic retention. Ophthalmol. Plast. Reconstr. Surg. 5:27, 1989.
22. Migliori, M. E., and Putterman, A. M.: Recurrent Jones tube extrusions successfully treated with a modified glass tube. Ophthalmol. Plast. Reconstr. Surg. 5:189, 1989.
23. Steinsapir, K. D., Glatt, H. J., and Putterman, A. M.: A 16-year study of conjunctival dacryocystorhinostomy. Am. J. Ophthalmol. 109:387, 1990.
24. Henderson, P. N.: A modified trephining technique for the insertion of Jones tube. Arch. Ophthalmol. 103:1582, 1985.
25. Banta, H. D., and Thacker, S. B.: The case for reassessment of health care technology. JAMA 264:235, 1990.
26. Foege, W. H.: Budgetary medical ethics. J. Public Health Policy 4:249, 1983.
27. Kulwin, D. R., Tiradellis, H., Levartovsky, S., Kersten, R. C., and Shumrick, K. A.: The value of intranasal surgery in assuring the success of a conjunctivodacryocystorhinostomy. Ophthalmol. Plast. Reconstr. Surg. 6:54, 1990.

Posterior Chamber Intraocular Lens Implantation in Eyes With Inactive and Active Proliferative Diabetic Retinopathy

Richard S. Ruiz, M.D., and Osman A. Saatci, M.D.

We reviewed the records of 2,100 consecutive eyes that had undergone extracapsular cataract extraction with intraocular lens implantation between January 1981 and December 1989. Of these eyes, 21 had inactive and four had active proliferative diabetic retinopathy at the time of cataract extraction. Twenty-one eyes with inactive proliferative diabetic retinopathy received extracapsular cataract extraction with posterior chamber intraocular lens implantation, and four eyes with active proliferative diabetic retinopathy had both extracapsular cataract extraction with posterior chamber intraocular lens implantation and pars plana vitrectomy with endophotocoagulation. The mean follow-up period was 27 months. Final visual acuity was 20/40 or better in 12 of 25 eyes (48%). Of 25 eyes, five (20%) showed progression of the retinopathy after the operation, and two (8%) developed macular edema. Extracapsular cataract extraction and posterior chamber intraocular lens implantation was well tolerated in most eyes.

THE MAIN RISKS of cataract surgery and intraocular lens implantation in patients with diabetes are progression of the retinopathy, development of rubeosis iridis, and difficulty in postoperative examination and photocoagulation. We studied 21 eyes with inactive and four eyes with active proliferative diabetic retinopathy that had undergone extracapsular cataract extraction and implantation of sulcus-fixated posterior chamber intraocular lenses.

Accepted for publication Nov. 9, 1990.

From the Department of Ophthalmology, Hermann Eye Center, University of Texas Medical School, Houston, Texas.

Reprint requests to Richard S. Ruiz, M.D., Hermann Eye Center, 6411 Fannin, 7th Fl., Houston, TX 77030.

Patients and Methods

We reviewed the records of 2,100 consecutive eyes that had extracapsular cataract extraction with intraocular lens implantation between January 1981 and December 1989 for the presence of proliferative diabetic retinopathy at the time of the cataract operation. Only eyes with a minimum of six months of postoperative follow-up were considered for analysis.

Information recorded before surgery included age, sex, duration of diabetes, type of diabetes, best-corrected visual acuity, presence of rubeosis iridis, previous panretinal photocoagulation or vitreoretinal surgery, and status of diabetic retinopathy in the fellow eye.

The type of surgery and the intraoperative complications were noted. Our standard extracapsular cataract extraction technique was used in all cases. A limbal-based conjunctival flap and a 10-mm grooved incision were created, followed by a large anterior capsulotomy to the anterior insertion of the zonules. The nucleus was dislocated with an irrigating cannula and delivered with a lens loop. The cortex was aspirated, and the capsule was polished. A posterior chamber intraocular lens was placed in the ciliary sulcus. If there was significant coexistent vitreous hemorrhage, a pars plana vitrectomy with endophotocoagulation was carried out immediately after the cataract surgery.

Postoperative data included most recent visual acuity, any change in the status of the retinopathy, macular edema, opacification of the posterior capsule, additional surgical proce-

dures including YAG capsulotomy, and duration of follow-up.

Results

Twenty-five eyes of 19 patients were included. Age at the time of the cataract operation ranged from 27 to 73 years (mean, 56 years). Twelve patients were men and seven were women. Duration of diabetes ranged from nine to 40 years (mean, 23 years). Seventeen patients had insulin-dependent diabetes and two patients had noninsulin-dependent diabetes. Preoperatively, none of the eyes had rubeosis iridis. Of 25 eyes, 21 had complete panretinal photocoagulation without neovascularization; one had incomplete panretinal photocoagulation with vitreous hemorrhage; and three had no panretinal photocoagulation with vitreous hemorrhage. Three eyes had one pars plana vitrectomy; three eyes had one pars plana vitrectomy with scleral buckling; and two eyes had two pars plana vitrectomies. Of 13 fellow eyes, seven had complete panretinal photocoagulation, two had background diabetic retinopathy, one had neovascular glaucoma, and three had phthisis bulbi. Best-corrected visual acuity before surgery and the most recent postoperative visual acuity are shown in the Figure.

Twenty-one eyes with previous panretinal photocoagulation and no active neovascular proliferation or hemorrhage were considered as having inactive proliferative diabetic retinopathy. In one of these eyes, the retinopathy was considered inactive although the fundus could not be examined because of a dense cataract. Ultrasonography, however, showed proliferation in the vitreous cavity. Four eyes that had preoperative vitreous hemorrhage and no previous photocoagulation or incomplete panretinal photocoagulation were considered to have active proliferative diabetic retinopathy.

Twenty-one eyes had extracapsular cataract extraction with posterior chamber lens implantation and four eyes had extracapsular cataract extraction with posterior chamber lens implantation and pars plana vitrectomy with panretinal endophotocoagulation. Posterior capsular rupture without vitreous loss occurred in two eyes. In one eye, a capsulotomy was performed at the time of the operation.

Of 25 eyes, 12 (48%) attained visual acuity of 20/40 or better (Figure). Of the 13 eyes with visual acuity of 20/50 or worse, two had macular edema, two had preretinal membranes, two had macular holes, two had optic atrophy, one had diabetic maculopathy, one had a vitreous hemorrhage, one had a disciform scar, one was enucleated, and one had clear media with no known cause for the decreased vision.

Four eyes of three patients with inactive proliferative diabetic retinopathy developed new areas or progression of neovascularization. Three of these eyes received additional photo-

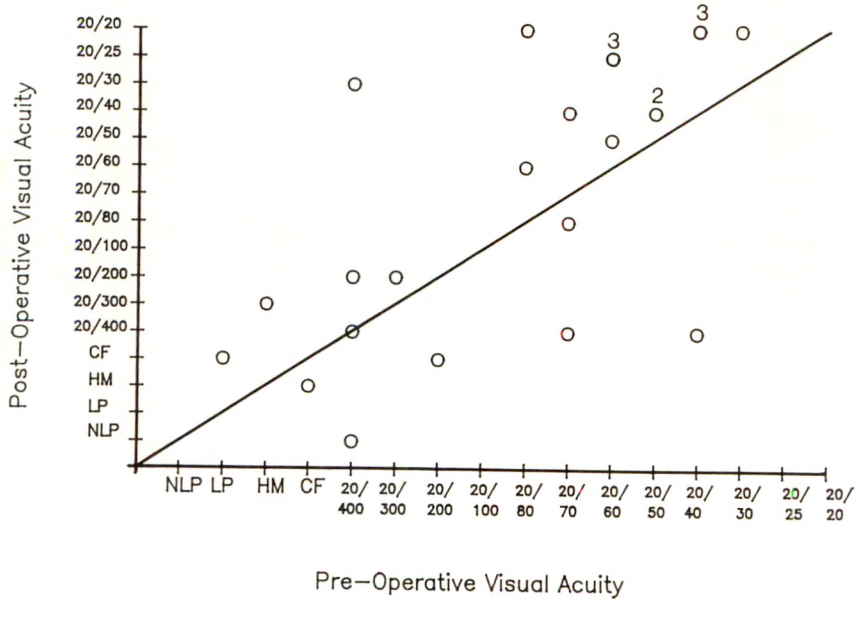


Figure (Ruiz and Saatci). Scattergram of best-corrected visual acuity before cataract surgery and most recent postoperative visual acuity. NLP indicates no light perception; LP indicates light perception; HM indicates hand motions; and CF indicates counting fingers.

coagulation postoperatively and underwent pars plana vitrectomy later with supplemental scattered endophotocoagulation because of recurrent and persistent vitreous hemorrhages. After treatment, there was no progression of the retinopathy. The eye with a dense cataract and ultrasonographic findings of proliferation in the vitreous developed rubeosis iridis and a tractional retinal detachment 11 months postoperatively. Despite medical treatment with atropine and corticosteroid eyedrops, extensive posterior synechiae developed, and an argon laser iridotomy was necessary to relieve pupillary block. Further photocoagulation was not possible because of extremely poor visualization of the fundus. Phthisis bulbi developed, and the eye was enucleated 49 months after cataract surgery.

Three of the four eyes with active proliferative diabetic retinopathy that underwent the combined procedure did not show progression of the retinopathy postoperatively. One eye developed recurrent vitreous bleeding after the surgery and was lost to follow-up. Two eyes of one patient with inactive proliferative diabetic retinopathy developed macular edema three and five months postoperatively. One eye had undergone YAG laser capsulotomy before the development of macular edema, whereas the other eye had an intact capsule. One eye developed diabetic maculopathy four years postoperatively and was treated by focal laser treatment.

The posterior capsule became opaque in ten of 24 eyes (41.7%). YAG laser capsulotomy was performed two to 14 months after the cataract surgery (mean, seven months). One eye underwent capsulotomy and then developed macular edema. The eye that developed rubeosis iridis received YAG laser capsulotomy in the seventh postoperative month.

The follow-up period ranged from six to 74 months (mean, 27 months). There was a minimum follow-up period of 12 months in 19 of 25 eyes (76%).

Discussion

After cataract surgery, visual rehabilitation is superior with the use of intraocular lenses as compared to aphakic spectacles or contact lenses. The optical disadvantages of peripheral field constriction and distortion with aphakic spectacle correction are intensified in the presence of diabetic macular disease and extensive panretinal photocoagulation.[1] Contact lens wear in patients with diabetes is often complicated by diminished tear production, reduced corneal sensitivity, and recurrent epithelial erosion.[2]

The preoperative status of the retinopathy,[3-6] the type of cataract extraction,[5-9] and the type of intraocular lens used[5,6,10] are factors influencing the outcome of cataract surgery in patients with diabetes. Eyes with minimal background retinopathy or no retinopathy have an excellent prognosis after cataract surgery with intraocular lens implantation.[3,4,11,12] Fung[10] reported that of ten eyes that had quiescent proliferative diabetic retinopathy preoperatively, four eyes required pars plana vitrectomy and one eye required additional laser therapy after phacoemulsification with posterior chamber intraocular lens implantation.[10] One eye developed rubeosis iridis and inoperable retinal detachment. In our series, four eyes of three patients in a group of 21 eyes with inactive proliferative diabetic retinopathy preoperatively developed further neovascularization. One of these eyes developed rubeosis iridis and tractional retinal detachment.

Apple and associates[13] described five patients with diabetes with preoperative preproliferative and proliferative diabetic retinopathy in whom severe visual loss with vitreous hemorrhage and neovascular glaucoma developed within six months after extracapsular cataract extraction with intraocular lens implantation. Pavase and Insler[14] described four eyes with no diabetic retinopathy or nonproliferative diabetic retinopathy before extracapsular cataract extraction with posterior chamber intraocular lens implants with a rapid progression to proliferative diabetic retinopathy, whereas the fellow eyes showed no progression. Prasad, Setna, and Dunne[15] reported similar findings in two eyes. Our study indicates that even in eyes with laser-ablated retinas, the retinopathy may progress after extracapsular cataract extraction with posterior chamber intraocular lens implantation. It is not clear whether the progression is directly caused by cataract extraction or by the natural course of the diabetic retinopathy, which may wax and wane.

One of the four eyes that underwent an extracapsular cataract extraction with posterior chamber intraocular lens implantation and pars plana vitrectomy with endophotocoagulation had recurrent vitreous hemorrhage postopera-

tively but was lost to follow-up. Three eyes showed no progression of retinopathy. Kokame, Flynn, and Blankenship[1] described six eyes that had undergone extracapsular cataract extraction with posterior chamber lens implantation and pars plana vitrectomy. Only one eye required further photocoagulation and pars plana vitrectomy with supplemental endophotocoagulation. They reported that all six eyes showed no progression of retinopathy ultimately.

One of our patients developed bilateral macular edema three and five months after the operation, and one eye developed diabetic maculopathy four years after the operation. The maculopathy was treated with focal laser photocoagulation. Alpar[5] reported a clinical cystoid macular edema rate of 13.3% in diabetic eyes that had undergone extracapsular cataract extraction with sulcus-fixated posterior chamber lens implantation. Jaffe and Burton[16] also indicated that progression of background diabetic retinopathy to a severe exudative form might develop in some patients. We believe that macular edema is one of the most important factors limiting the visual outcome in these patients. Two eyes in our series with macular edema had visual acuity of counting fingers and 20/200.

Although the influence of the severity of the preoperative diabetic retinopathy on the postoperative visual outcome is not completely understood, the influence of the type of cataract extraction is clear. The risk for rubeosis iridis and subsequent neovascular glaucoma is higher in intracapsular cataract extraction compared with extracapsular cataract surgery.[7,9] Aiello, Wand, and Liang[7] studied 154 patients with diabetes who underwent unilateral intracapsular cataract extraction. The fellow eyes were used as controls. They reported a 7.8% overall incidence of rubeosis iridis without regard to the degree of preoperative retinopathy. In 216 eyes studied after cataract extraction, Poliner and associates[9] found neovascular glaucoma in cases with intracapsular cataract surgery and extracapsular cataract surgery with primary capsulotomy but none in extracapsular cataract extractions with intact posterior capsules.

In our series, visualization was satisfactory for ophthalmoscopy, photocoagulation, and pars plana vitrectomy when necessary in all eyes but one. Other studies have concluded that ophthalmic examination, photography, and laser treatment are not affected by the presence of intraocular lenses.[10,12] Thompson, Kritzinger, and Ropper Hall[17] argued that iris-clip lenses should not be regarded as a contraindication in some patients with diabetes. It is still wise to avoid an intraocular lens procedure that will make adequate dilation of the pupil unsafe.[18]

In our study, ten of 24 eyes (41.7%) required YAG laser capsulotomy because of opacification of the capsule. The posterior capsulotomy rate in patients followed up for three years has been reported to range from 5.6%[19] to 50%.[20] Percival and Setty[19] argued that the incidence of capsular fibrosis might be increased in diabetic eyes. Liesegang, Bourne, and Ilstrup[21] stated that the mean time from cataract surgery to posterior capsulotomy in patients with diabetes was not statistically different from that found in nondiabetic control patients. We believe that there may be an increased tendency for capsular opacification in patients with diabetes. There was no significant correlation between YAG capsulotomy and progression of retinopathy in our patients.

Our study indicates that extracapsular cataract extraction with posterior chamber lens implantation with or without pars plana vitrectomy in the presence of both inactive and active proliferative diabetic retinopathy is well tolerated in most patients. Progression of retinopathy may occur after extracapsular cataract extraction with posterior chamber lens implantation; and therefore, patients with inactive as well as active proliferative diabetic retinopathy should be followed up frequently and prudently. It is necessary to examine adequately the fundus postoperatively, and it may be necessary to administer laser treatment. For this reason, we recommend a large anterior capsulotomy to the anterior zonular insertion and surgical creation of an adequate pupillary opening in those eyes in which the pupil will not dilate.

References

1. Kokame, G. T., Flynn, H. W., Jr., and Blankenship, G. W.: Posterior chamber intraocular lens implantation during diabetic pars plana vitrectomy. Ophthalmology 96:603, 1989.

2. Schultz, R. O., Van Horn, D. L., Peters, M. A., Klewin, K. M., and Schutten, W. H.: Diabetic keratopathy. Trans. Am. Ophthalmol. Soc. 79:180, 1981.

3. Clayman, H. M., Jaffe, N. S., and Light, D. S.: Lens implantation and diabetes mellitus. Am. J. Ophthalmol. 88:990, 1979.

4. Straatsma, B. R., Pettit, T. H., Wheeler, N., and Miyamasu, W.: Diabetes mellitus and intraocular lens implantation. Ophthalmology 90:336, 1983.

5. Alpar, J. J.: Diabetes. Cataract extraction and intraocular lenses. J. Cataract Refract. Surg. 13:43, 1987.

6. Levin, M. L., Kincaid, M. C., Eifler, C. W., Holt, J. E., Speight, J. W., and O'Connor, P. S.: Effect of cataract surgery and intraocular lenses on diabetic retinopathy. J. Cataract Refract. Surg. 14:642, 1988.

7. Aiello, L. M., Wand, M., and Liang, G.: Neovascular glaucoma and vitreous hemorrhage following cataract surgery in patients with diabetes mellitus. Ophthalmology 90:814, 1983.

8. Williams, G. A., Eisenstein, R., Schumacher, B., Hsiao, K.-C., and Grant, D.: Inhibitor of vascular endothelial cell growth in the lens. Am. J. Ophthalmol. 97:366, 1984.

9. Poliner, L. S., Christianson, D. J., Escoffery, R. F., Kolker, A. E., and Gordon, M. E.: Neovascular glaucoma after intracapsular and extracapsular extraction in diabetic patients. Am. J. Ophthalmol. 100:637, 1985.

10. Fung, W. E.: Phacoemulsificaton and implantation of posterior chamber intraocular lens in eyes with quiescent proliferative diabetic retinopathy. Graefes Arch. Clin. Exp. Ophthalmol. 225:251, 1987.

11. Sebestyen, J. G., and Wafai, M. Z.: Experience with intraocular lens implants in patients with diabetes. Am. J. Ophthalmol. 96:94, 1983.

12. Sebestyen, J. G.: Intraocular lenses and diabetes mellitus. Am. J. Ophthalmol. 101:425, 1986.

13. Apple, D. J., Mamalis, N., Lotfield, K., Googe, J. M., Novak, L. C., Kavka-Van Norman, D., Brady, S. E., and Olson, R. J.: Complications of intraocular lenses. A historical and histopathological review. Surv. Ophthalmol. 29:1, 1984.

14. Pavase, T., and Insler, M. S.: Effects of extracapsular cataract extraction with posterior chamber lens implantation on the development of neovascular glaucoma in diabetics. J. Cataract Refract. Surg. 13:197, 1987.

15. Prasad, P., Setna, P. H., and Dunne, J. A.: Accelerated ocular neovascularization in diabetics following posterior chamber lens implantation. Br. J. Ophthalmol. 74:313, 1990.

16. Jaffe, G. J., and Burton, T. C.: Progression of nonproliferative diabetic retinopathy following cataract extraction. Arch. Ophthalmol. 106:745, 1988.

17. Thompson, S. M., Kritzinger, E. E., and Ropper Hall, M. J.: Should diabetes be a contraindication for an intraocular lens? Trans. Ophthalmol. Soc. U.K. 103:115, 1983.

18. Patz, A.: Photocoagulation of retinal, vascular and macular diseases through intraocular lenses. Ophthalmology 88:398, 1981.

19. Percival, S. P. B., and Setty, S. S.: Analysis of the need for secondary capsulotomy during a five year follow-up. J. Cataract Refract. Surg. 14:379, 1988.

20. Wilhelmus, K. R., and Emery, J. M.: Posterior capsule opacification following phacoemulsification. Ophthalmic Surg. 11:264, 1980.

21. Liesegang, T. J., Bourne, W. M., and Ilstrup, D. M.: Secondary surgical and neodymium:YAG laser discissions. Am. J. Ophthalmol. 100:510, 1985.

Delayed-Onset Pseudophakic Endophthalmitis

Gregory M. Fox, M.D., Brian C. Joondeph, M.D., Harry W. Flynn, Jr., M.D., Stephen C. Pflugfelder, M.D., and Thomas J. Roussel, M.D.

We reviewed 19 cases of delayed-onset pseudophakic endophthalmitis in which diagnostic cultures were performed at one month or more after cataract extraction with posterior chamber intraocular lens implantation. We isolated four different organisms in these 19 cases: 12 *Propionibacterium* species (63%), three *Candida parapsilosis* (16%), three *Staphylococcus epidermidis* (16%), and one *Corynebacterium* species (5%). Because of the unusual delayed-onset features of these cases and the retrospective nature of this study, a variety of treatment regimens were used. Twelve patients had recurrence of marked inflammation despite an apparent initial cure, and ten of these patients had positive culture results on repeat examination of intraocular fluids. Nine patients continued to be treated with topical corticosteroids postoperatively to suppress low-grade inflammation. Of the 19 patients, 16 had final visual acuity of 20/400 or better. Delayed-onset pseudophakic endophthalmitis had a more favorable visual prognosis, compared to acute-onset endophthalmitis.

INFECTIOUS ENDOPHTHALMITIS is an uncommon complication after cataract surgery and intraocular lens implantation. Although this condition typically occurs in the early postoperative period, a less common manifestation of postoperative endophthalmitis has a chronic course with recurrent low-grade inflammation and has been called chronic bacterial endophthalmitis.[1] Even though *Propionibacterium acnes* is a frequent etiologic agent in this category of postoperative endophthalmitis,[2-6] delayed-onset pseudophakic endophthalmitis is not always caused by *P. acnes*. In 19 culture-proven cases of delayed-onset pseudophakic endophthalmitis, we studied the spectrum of organisms and the distinguishing clinical features of these infections. Based upon our experience in the management of these cases, specific treatment options are discussed.

Patients and Methods

We reviewed the microbiology laboratory files and corresponding clinical records of 187 patients who had culture-proven endophthalmitis after extracapsular cataract extraction with placement of a posterior chamber intraocular lens. All patients were examined at our institution between November 1979 and June 1989. Charts were reviewed for the timing of the onset of symptoms, previous topical antibiotic or corticosteroid treatment, and initial clinical manifestation. Follow-up information after treatment was obtained through May 1990 from the medical records or from the referring physicians and included final visual acuity, intraocular pressure, and any observed complications.

Of the 187 patients with pseudophakic endophthalmitis in this ten-year period, 127 had diagnostic cultures performed in the first four weeks after cataract extraction. Of these 127 patients, 120 had positive cultures of intraocular specimens obtained during the first two weeks. Seven patients underwent vitreous tap during the third week after cataract surgery, and in two patients these infections were associated with suture removal or vitreous wick syndrome.

Of the 187 patients, 60 had the initial diagnostic procedure performed one month after extracapsular cataract surgery. One month was selected as a dividing line between early and delayed-onset pseudophakic endophthalmitis. Of the 60 patients with delayed-onset pseudophakic endophthalmitis, we excluded 26 pa-

Accepted for publication Sept. 18, 1990.

From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida. This study was supported in part by Fight For Sight, Inc. This study was presented in part at the 23rd Annual Meeting of the Retina Society, Key Largo, Florida, Oct. 5, 1990.

Reprint requests to Harry W. Flynn, Jr., M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

tients with acute bleb-associated endophthalmitis, six patients with recent postoperative suture removal, six patients with traumatic wound dehiscences, and one critically ill patient with septicemia who developed endogenous bacterial endophthalmitis. Two of these 60 patients with positive intraocular cultures performed in our microbiology laboratory were treated by physicians at another hospital and were excluded because of inadequate information regarding their clinical course and treatment. In one of these two patients, both *Actinomyces israelii* and *P. acnes* were cultured from the vitreous, and this patient attained final visual acuity of counting fingers. *Propionibacterium acnes* was cultured from the aqueous specimen of the other patient. This second patient, described by Brady, Cohen, and Fischer,[7] attained final visual acuity of 20/20 with follow-up at another hospital. The remaining 19 patients with clinical endophthalmitis and diagnostic intraocular cultures performed one month after extracapsular cataract extraction and posterior chamber intraocular lens implantation met our criteria for delayed-onset pseudophakic endophthalmitis. Of these 19 patients, four (Cases 1, 7, 11, and 12; Table 1) have been previously described by Zambrano and associates.[5]

Intraocular specimens were obtained from all patients and were inoculated into appropriate culture media.[8-10] Our criteria for a positive culture were the following: growth of the same organism on two or more media; or semiconfluent growth on one solid medium; or growth at the inoculation site on a medium and confirmed by organisms seen on Gram stain or histologic examination of intraocular tissues. All patients met these criteria for positive culture, except for three patients in whom *Propionibacterium* species grew from thioglycolate medium only but who had the typical clinical features of *P. acnes* endophthalmitis[3] (Cases 8, 10, and 11; Table 1).

Results

The spectrum of causative organisms in these patients with delayed-onset pseudophakic endophthalmitis is shown in Table 1. The culture reports indicated that of the 19 cases, 12 (63%) were caused by *Propionibacterium* species (one by *P. arachnia* and 11 by *P. acnes*); three cases (16%) were caused by *Candida parapsilosis*; three cases (16%) were caused by *Staphylococcus epidermidis*; and the remaining case (5%) was caused by a *Corynebacterium* species.

The vitreous was culture-positive in all 19 patients. The anterior chamber fluid was cultured in six patients and was positive in five of these patients. Gram stains of the initial intraocular specimen were positive in only one of 12 patients with *Propionibacterium* species infection, in one of three patients with *C. parapsilosis* infection, in two of three patients with *S. epidermidis* endophthalmitis, and in the patient with *Corynebacterium* species endophthalmitis.

Review of the clinical course of these 19 patients showed that recurrent episodes of postoperative inflammation were typical of all patients. In the patients with *Propionibacterium* species infection, the time of diagnosis by positive culture of intraocular fluid averaged eight months and ranged from six weeks to 36 months after surgery. The other cases were confirmed by positive cultures at variable times after cataract surgery (*C. parapsilosis*, one month to 23 months; *S. epidermidis*, one to three months; and *Corynebacterium* species, two months).

All patients were referred by anterior segment surgeons for treatment. Many of these patients were noted to have corticosteroid-responsive iritis, vitreitis, or both, before their referral. Continued topical corticosteroid treatment of presumed sterile intraocular inflammation delayed the diagnosis in 15 of 19 patients. Ten of 12 patients with *Propionibacterium* species infection (all except Cases 1 and 10), all three patients with *S. epidermidis* infection, and the patient with *Corynebacterium* endophthalmitis had reduced or stable intraocular inflammation for a variable length of time while taking topical corticosteroids. However, only one of the three patients with fungal endophthalmitis (Case 19) clinically improved while taking topical corticosteroids.

All 12 patients with *Propionibacterium* species endophthalmitis demonstrated a prominent white plaque within the capsule (Fig. 1) and vitreitis (Table 1). Chronic granulomatous inflammation and keratic precipitates were noted in six of the 12 patients. Beaded fibrin strands extending across the anterior chamber were seen in two patients (Cases 10 and 11). Eight patients with *Propionibacterium* species endophthalmitis had initial visual acuity of 20/200 or better. A subset of two patients (Cases 2 and 5), however, initially had more

TABLE 1
CLINICAL FEATURES ON INITIAL EXAMINATION

CASE NO., AGE (YRS), SEX	ORGANISM CULTURED	TIME FROM CATARACT EXTRACTION TO ONSET OF SYMPTOMS	TIME FROM CATARACT EXTRACTION TO DIAGNOSTIC CULTURE	INITIAL VISUAL ACUITY*	CLINICAL FEATURES	INITIAL INFLAMMATION IMPROVED OR STABILIZED WITH TOPICAL CORTICOSTEROIDS
1, 63, F†	*P. acnes*	6 wks	6 wks	20/200	White plaque, hypopyon, vitreitis	No
2, 73, M	*P. acnes*	4 mos	11 mos	LP	White plaque, hypopyon, vitreitis	Yes
3, 77, F	*P. acnes*	4 mos	13 mos	20/30	White plaque, keratic precipitates, vitreitis	Yes
4, 75, M	*P. acnes*	2 wks	4 mos	20/200	White plaque, keratic precipitates, vitreitis	Yes
5, 75, F	*P. arachnia*	6 wks	3 mos	HM	White plaque, keratic precipitates, hypopyon, vitreitis	Yes
6, 62, M	*P. acnes*	4 mos	21 mos	20/200	White plaque, vitreitis	Yes
7, 74, M†	*P. acnes*	8 mos	36 mos	20/100	White plaque, hypopyon, vitreitis	Yes
8, 57, M	*P. acnes*‡	2 mos	5 mos	20/70	White plaque, keratic precipitates, vitreitis	Yes
9, 76, M	*P. acnes*	2 wks	6 wks	20/200	White plaque, fibrin in anterior chamber, vitreitis	Yes
10, 76, F	*P. acnes*‡	2 mos	12 mos	HM	White plaque, keratic precipitates, beaded strands, vitreitis, central retinal vein occlusion	Not given
11, 81, M†	*P. acnes*‡	2 mos	24 mos	HM	White plaque, keratic precipitates, beaded strands, vitreitis, central retinal vein occlusion	Yes
12, 68, M†	*P. acnes*	2 wks	4 mos	20/100	White plaque, vitreitis	Yes
13, 75, F	*S. epidermidis*	5 days	6 wks	1/200	Fibrin in anterior chamber, dense vitreitis	Yes
14, 71, M	*S. epidermidis*	1 mo	3 mos	3/200	Hypopyon, keratic precipitates, dense vitreitis	Yes
15, 78, M	*S. epidermidis*	2 days	1 mo	LP	Keratic precipitates, fibrin in anterior chamber, dense vitreitis	Yes
16, 91, F	*Corynebacterium*	6 wks	2 mos	LP	White plaque, hypopyon, dense vitreitis	Yes
17, 81, M	*C. parapsilosis*	3 days	2 mos	20/300	Keratic precipitates, isolated vitreous infiltrates, vitreitis	No
18, 76, M	*C. parapsilosis*	3 days	1 mo	20/60	Keratic precipitates, isolated vitreous infiltrates, vitreitis	Not given
19, 66, M	*C. parapsilosis*	2 mos	23 mos	20/25	White plaque, keratic precipitates, isolated vitreous infiltrates, vitreitis	Yes

* LP indicates light perception and HM indicates hand motions.
† Cases have been reported previously in reference 5 (Cases 1, 7, 11, and 12).
‡ Equivocal culture growth found in Cases 8, 10, and 11.

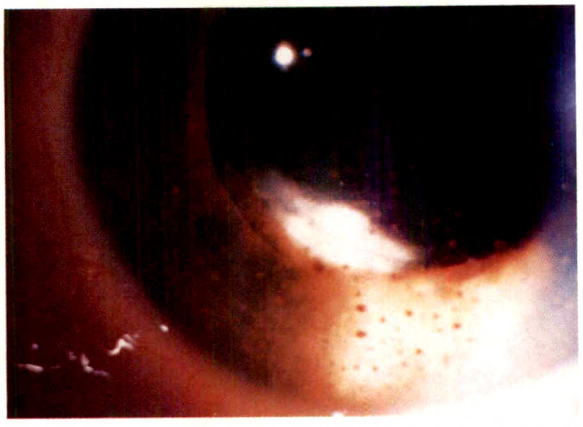


Fig. 1 (Fox and associates). Case 4. *Propionibacterium acnes* endophthalmitis on initial examination demonstrating a prominent white plaque within the capsule and inferior keratic precipitates.



Fig. 2 (Fox and associates). Case 18. *Candida parapsilosis* endophthalmitis on initial examination demonstrating stringy, isolated, white infiltrates in the anterior vitreous adjacent to capsular remnants.

advanced intraocular inflammation, including hypopyon, vitreitis, and visual acuity of hand motions or worse. The remaining two patients with poor initial visual acuity (Cases 10 and 11) had diffuse intraretinal hemorrhages resembling a central retinal vein occlusion at the time of the initial diagnosis.

All patients with infections caused by *S. epidermidis* had marked anterior chamber inflammation, but only one patient had hypopyon formation (Case 14). A white intracapsular plaque was not observed in any of these patients, but dense vitreitis was noted in all three patients. In these three patients, initial visual acuity varied from light perception to 3/200.

The patient with *Corynebacterium* species infection (Case 16) initially had marked anterior chamber inflammation, hypopyon, and dense vitreitis. A white plaque adjacent to the posterior capsule was also noted. Initial visual acuity was light perception.

Similar to the patients with *Propionibacterium* species infection, all patients with chronic fungal endophthalmitis had a variable decrease of visual acuity ranging from 20/25 to 20/300 on initial manifestation. These infections were characterized at some point during their clinical course by localized white infiltrates in the anterior vitreous adjacent to the capsule (Fig. 2). A white plaque inside the posterior capsule, resembling those seen in *Propionibacterium* species endophthalmitis, was observed in one of three patients (Case 19). Granulomatous anterior segment inflammation was seen initially in only two of the three patients (Cases 17 and 18), and the third patient (Case 19) developed granulomatous inflammation later during recurrent episodes of infection.

Five patients with *Propionibacterium* species infection were treated initially with intraocular antibiotics alone (Cases 1, 4, 7, 8, and 12; Table 2). Because of suspected recurrent infection, four of these five patients had further surgery. Three patients had pars plana vitrectomy and central capsulectomy, including removal of the area of the white plaque and repeat injection of intraocular antibiotics during the follow-up course. The fourth patient had complete capsule removal and intraocular lens exchange. Vitreous specimens taken during the second operative procedure in these four patients were still positive for *Propionibacterium* species despite previous treatment. All five of these patients attained final visual acuity of 20/400 or better.

Of the 12 patients with *Propionibacterium* species infections, six (Cases 2, 3, 5, 6, 9, and 10; Table 2) were initially treated with a standard three-port vitrectomy, central capsulectomy with selective removal of the area of white plaque, and injection of intraocular antibiotics. One of these six patients (Case 3) had recurrent inflammation and documented recurrent infection. An anterior vitrectomy, complete capsule removal using alpha-chymotrypsin, and intraocular lens exchange with repeat intravitreal antibiotics were performed in this patient. The cultures of removed capsular remnants were positive for *P. acnes*. Of the six patients with *Propionibacterium* species infection treated with initial vitrectomy, five of six attained final visual acuity of 20/400 or better. One patient

TABLE 2
TREATMENT AND FINAL VISUAL RESULTS

CASE NO., ORGANISM	INITIAL TREATMENT		FOLLOW-UP TREATMENT		FINAL VISUAL ACUITY†	FOLLOW-UP (MOS)
	INTRAOCULAR ANTIBIOTICS* (INTRAOCULAR CORTICOSTEROIDS)	SURGERY	INTRAOCULAR ANTIBIOTICS* (INTRAOCULAR CORTICOSTEROIDS)	SURGERY		
1, *P. acnes*	Vancomycin, tobramycin (No)	Vitreous aspiration	None	None	20/40	6
2, *P. acnes*	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	None	None	LP	10
3, *P. acnes*	Vancomycin (Yes)	Pars plana vitrectomy, central capsulectomy	Vancomycin (No)	Anterior vitrectomy, intraocular lens exchange	20/60	6
4, *P. acnes*	Vancomycin (Yes)	Vitreous tap	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	20/100	4
5, *P. arachnia*	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	None	None	20/30	15
6, *P. acnes*	None (No)	Pars plana vitrectomy, intraocular lens exchange	None	None	20/20	13
7, *P. acnes*	Vancomycin, tobramycin (No)	Vitreous tap	Cefazolin (No)	Pars plana vitrectomy, central capsulectomy	20/30	16
8, *P. acnes*	Vancomycin, tobramycin (No)	Vitreous tap	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	20/20	10
9, *P. acnes*	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	None	None	20/40	18
10, *P. acnes*	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	None	None	20/400	12
11, *P. acnes*	Vancomycin, tobramycin (No)	Two-port subtotal pars plana vitrectomy	Vancomycin, gentamicin (Yes)	Three-port more complete pars plana vitrectomy, central capsulectomy	20/100	48
12, *P. acnes*	Cefazolin, gentamicin (No)	Vitreous aspiration, pars plana vitrectomy, central capsulectomy	No intraocular antibiotics	Intraocular lens exchange	20/30	36
13, *S. epidermidis*	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	None	None	20/40	9
14, *S. epidermidis*	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	None	None	20/70	3
15, *S. epidermidis*	Vancomycin, gentamicin (No)	Two-port subtotal pars plana vitrectomy	Vancomycin (Yes)	Three-port pars plana vitrectomy, central capsulectomy	20/25	7

Continued on pg 168

TABLE 2 (*continued*)
TREATMENT AND FINAL VISUAL RESULTS

CASE NO., ORGANISM	INITIAL TREATMENT		FOLLOW-UP TREATMENT		FINAL VISUAL ACUITY†	FOLLOW-UP (MOS)
	INTRAOCULAR ANTIBIOTICS* (INTRAOCULAR CORTICOSTEROIDS)	SURGERY	INTRAOCULAR ANTIBIOTICS* (INTRAOCULAR CORTICOSTEROIDS)	SURGERY		
16, *Corynebacterium*	Cefazolin, gentamicin (No)	Vitreous aspiration	Vancomycin (No)	Pars plana vitrectomy, central capsulectomy	HM	4
17, *C. parapsilosis*	Amphotericin B (No)	Pars plana vitrectomy, central capsulectomy	Amphotericin B ×2 (No)	Pars plana vitrectomy, central capsulectomy (×2)	HM	12
18, *C. parapsilosis*	Amphotericin B (No)	Pars plana vitrectomy, central capsulectomy	Amphotericin B (No)	None	20/70	60
19, *C. parapsilosis*	Amphotericin B (No)	Pars plana vitrectomy, central capsulectomy	Amphotericin B ×2 (No)	Pars plana vitrectomy, capsulectomy, and intraocular lens removal	20/25	7

*Dose of intraocular antibiotic or antifungal agents: vancomycin, 1 mg; cefazolin, 2.25 mg; gentamicin, 0.1 mg; tobramycin, 0.1 mg; and amphotericin B, 5 μg.

†LP indicates light perception and HM indicates hand motions.

(Case 2) had final visual acuity of light perception because of optic atrophy, neovascular glaucoma, and proliferative diabetic retinopathy.

One patient with *Propionibacterium* species infection (Case 11, Table 2) was treated initially with a subtotal two-port vitrectomy with injection of intraocular antibiotics. Because of recurrent inflammation, a more complete three-port vitrectomy, central capsulectomy, and repeat injection of intraocular antibiotics were performed. *Propionibacterium acnes* was again cultured from the vitrectomy specimen. This patient attained final visual acuity of 20/100.

Because of the high rate of recurrent infection, the determination of a clinical cure was difficult in these patients with *Propionibacterium* species infection (Table 3). In total, six of 12 patients continued to use topical corticosteroids on long-term follow-up (Cases 2 through 5, 8, and 9). Despite the recurrences of inflammation in the patients with *Propionibacterium* species infection, 11 of 12 patients attained final visual acuity of 20/400 or better. Seven of 12 patients had visual acuity of 20/50 or better.

Because of the dense vitreous infiltrates at the initial examination, all three patients with *S. epidermidis* infection were treated by pars plana vitrectomy and injection of intraocular antibiotics. With follow-up of three to nine months, the three patients attained visual acuity of 20/25, 20/40, and 20/70, respectively. One of these patients (Case 15, Table 2) had marked recurrent inflammation, including vitreitis, anterior uveitis, hypopyon, and visual acuity of hand motions, one month after initial presumed successful treatment with a subtotal vitrectomy without capsulectomy and injection of intraocular antibiotics. A more complete three-port pars plana vitrectomy with central capsulectomy and repeat injection of intraocular antibiotics and corticosteroids was performed. The repeat cultures of the vitreous specimen were negative. Final visual acuity in this patient was 20/25.

The patient with *Corynebacterium* species infection was initially treated with vitreous tap and intraocular antibiotics. Visual acuity remained hand motions because of persistent media opacities. When visual acuity decreased to light perception only and intraocular pressure by applanation tonometry decreased to 1 mm Hg, a pars plana vitrectomy was performed two months after the initial treatment. The eye developed increasing inflammation six months after vitrectomy, and repeat vitreous tap was recommended. The patient refused further treatment, and visual acuity remained hand motions with hypotony.

TABLE 3
ENDOPHTHALMITIS RECURRENCES

CASE NO.	NO. OF EPISODES OF RECURRENCE	REPEAT CULTURE RESULT*	LONG-TERM TOPICAL CORTICOSTEROIDS	COMMENTS
1	0	None	No	No recurrent inflammation
2	0	None	Yes	Proliferative diabetic retinopathy, neovascular glaucoma
3	1	Positive	Yes	Recurred after pars plana vitrectomy, capsulectomy, and intraocular antibiotics
4	1	Positive	Yes	Recurred after vitreous tap and intraocular antibiotics; age-related macular degeneration
5	1	Not performed	Yes	Recurrent anterior uveitis treated with topical corticosteroids
6	0	None	No	No recurrent inflammation
7	1	Positive	No	Recurred after vitreous tap and intraocular antibiotics
8	1	Positive	Yes	Recurred after vitreous tap and intraocular antibiotics
9	0	None	Yes	Intermittent episodes of intraocular inflammation
10	0	None	No	Central retinal vein occlusion
11	1	Positive	No	Recurred after subtotal pars plana vitrectomy and intraocular antibiotics; central retinal vein occlusion
12	1	Positive	No	Recurred after vitreous tap and intraocular antibiotics
13	0	None	No	No recurrent inflammation
14	0	None	No	Macular hole
15	1	Negative	Yes	Culture negative recurrence 1 month after apparent cure
16	2	Positive both times	Yes	Recurred after vitreous tap and intraocular antibiotics; suspected recurrence after pars plana vitrectomy; patient refused further treatment
17	2	Positive both times	No	Recurred after two pars plana vitrectomies; endstage chronic open-angle glaucoma
18	1	Positive	No	Recurred after pars plana vitrectomy
19	2	Positive both times	Yes	Recurred after two pars plana vitrectomies; required intraocular lens removal

* Repeat positive culture results were the same organism as initially cultured in all cases.

All three patients with endophthalmitis caused by *C. parapsilosis* had recurrent post-treatment inflammation and repeat culture-proven persistent infection after initial apparent cure with vitrectomy and intraocular amphotericin B. One patient (Case 17) received a repeat amphotericin B injection (5 μg), at the time of the second vitrectomy procedure. Five months after the third vitrectomy procedure, the patient required filtering surgery and had final visual acuity of hand motions because of endstage glaucoma. Another patient (Case 18) had two vitrectomy procedures (each including 5 μg of amphotericin B) and attained visual acuity of 20/70, with five years of follow-up after the second vitrectomy. One patient (Case 19) required pars plana vitrectomy twice and intraocular amphotericin B injection three times. Despite these procedures, this patient had increasing inflammation in the vitreous base region, which necessitated intraocular lens removal and complete capsulectomy using alpha-chymotrypsin. This patient (Case 19) attained final visual acuity of 20/25 with seven months of follow-up since the last surgical treatment.

Discussion

Case reports or small series of patients with delayed-onset postoperative endophthalmitis caused by a variety of organisms, including *P. acnes*,[2-6] *P. granulosum*,[11] *S. aureus*,[12] *S. epidermidis*,[1] *Achromobacter* species,[1] *Cephalosporium* species,[13] *C. parapsilosis*,[14] *Acremonium* species,[15] *Paecilomyces* species,[15] and *Aspergillus* species[15] have been described. We have also previously reported a case of endophthalmitis

manifesting seven weeks after secondary intraocular lens implantation in which *Mycobacterium chelonae* was isolated.[16] In our patients with culture-proven infection after extracapsular cataract extraction and posterior chamber intraocular lens implantation examined at our institution between 1979 and 1989, four organisms in this chronic category were isolated: *P. acnes*, *C. parapsilosis*, *S. epidermidis*, and *Corynebacterium* species. This spectrum of infecting organisms in the delayed-onset pseudophakic endophthalmitis category differs from a previously published report from our institution, which reviewed primarily acute postoperative pseudophakic endophthalmitis.[17] Even though *S. epidermidis* was seen in both categories, *Staphylococcus* species (including *S. aureus*), streptococci, and gram-negative organisms were more frequently observed in the acute postoperative category.[9,10,17,18]

A syndrome of delayed-onset pseudophakic endophthalmitis manifesting with a white plaque, moderate visual loss, and often granulomatous inflammation after extracapsular cataract extraction caused by *P. acnes* was described by Meisler and associates[3] in 1986. Further reports have described the management options and final visual results of this syndrome.[4-7] Semel and associates[19] reported growth of *P. acnes* from the intraocular lens in four of 12 patients in whom the intraocular lenses were removed during routine keratoplasty for pseudophakic bullous keratopathy. Although this report did not identify *P. acnes* as an etiologic agent in pseudophakic bullous keratopathy, it does suggest that this organism can remain viable in the pseudophakic eye for an extended time.

Even though *Propionibacterium* species, *S. epidermidis*, and *C. parapsilosis* are now well-recognized ocular pathogens, *Corynebacterium* species have often been regarded as nonpathogenic contaminants of the human external eye. However, ocular infections caused by *Corynebacterium* species, including indolent keratitis[20] and endophthalmitis,[21] have been reported.

Endophthalmitis occurring months or years after surgery is a well-recognized complication of conjunctival filtering blebs.[22] Patients with bleb-associated endophthalmitis, however, typically have the acute onset of inflammation and are usually distinguished from these patients with delayed-onset pseudophakic endophthalmitis by the presence of an obviously infected filtering bleb. Furthermore, bleb-associated infections are generally caused by more virulent organisms, including either *Streptococcus* species or *Haemophilus* species, in 80% of reported culture-positive cases.[22]

Endophthalmitis cases occurring five and nine months after scleral buckling surgery have been reported.[23] Visible intrusion of the buckling element was suspected to be the access site of the infection. Vitreous cultures performed at the time of scleral buckle removal were positive for *Proteus mirabilis* in both cases. Late-onset endophthalmitis occurring months after retinal detachment surgery caused by such a virulent organism clearly represents a different entity compared to delayed-onset pseudophakic endophthalmitis in our series of patients.

These patients with delayed-onset pseudophakic endophthalmitis had several specific clinical features, which may help to distinguish between the different infecting organisms. A white intracapsular plaque, representing sequestered organisms within the capsule, was seen in all 12 of the patients with *Propionibacterium* species infection. In one patient with *C. parapsilosis* endophthalmitis and the patient with *Corynebacterium* species infection, however, a white intracapsular plaque was also observed. Granulomatous inflammation as manifested by large keratic precipitates was also seen in six of the 12 patients with *Propionibacterium* species infection. Beaded fibrin strands extending across to the anterior chamber were seen in two of the 12 patients with *Propionibacterium* species infection. Stringy white infiltrates in the anterior vitreous adjacent to the capsular remnants occurred in all three of the patients with *C. parapsilosis* infection. Dense vitreitis causing a poor view of fundus details was noted in all three patients with *S. epidermidis* endophthalmitis and the patient with *Corynebacterium* species infection. None of the patients with fungal or *P. acnes* infection had a diffuse, dense vitreitis, even though a mild cellular reaction in the vitreous was observed in all of these patients.

In these patients with delayed-onset pseudophakic endophthalmitis, the spectrum of organisms and the potential difficulty encountered in achieving a positive culture result emphasize the need for effective culture techniques. Anterior chamber and vitreous specimens from these cases can be placed on anaerobic plates and thioglycolate broth (ideal for *P. acnes*), Sabouraud's media (ideal for fungi), and blood agar and chocolate plates (ideal for *S. epidermidis* and *Corynebacterium* species). The use of blood culture bottles, a technique allow-

ing direct inoculation of unfiltered vitrectomy specimens,[24] was also successful in achieving a positive culture result in four of the six patients in whom they were used. In all culture methods, culture media should be observed for at least two weeks because of the slow growth of both *P. acnes*[5] and *Corynebacterium* species.[21]

Patients with delayed-onset pseudophakic endophthalmitis had better posttreatment visual acuity when compared to acute postoperative pseudophakic endophthalmitis.[9,10,17,18] Of 19 patients, 16 had final visual acuity of 20/400 or better. Of the three patients with visual acuity worse than 20/400, two patients had significant preexisting diseases (optic atrophy, neovascular glaucoma, and proliferative diabetic retinopathy in the patient in Case 2 and advanced open-angle glaucoma in the patient in Case 17). The patient with *Corynebacterium* species infection developed chronic hypotony and refused further treatment.

Because of the variable manifestations and limited treatment experience with this category of delayed-onset pseudophakic endophthalmitis, the ideal treatment remains controversial.[5] Several different approaches were selected by the surgeons of different subspecialities who treated these patients. In the five patients with *P. acnes* infection treated initially with injection of intraocular antibiotics without vitrectomy, recurrent infection occurred in four patients. Subsequent pars plana vitrectomy, central capsulectomy, and repeat intraocular antibiotic injection were performed in three patients, and complete capsule removal with intraocular lens exchange was performed in one patient. Despite apparent initial cure with pars plana vitrectomy and injection of intraocular antibiotics or antifungal agents, initial treatment failures also occurred in five of the 13 patients treated by this approach. Stern, Engel, and Driebe[25] have described similar patients with recurrent endophthalmitis who have required repeated injections of intraocular antibiotics with pars plana vitrectomy to achieve a clinical cure.

Alternative methods of treatment for patients with *Propionibacterium* species infection have been reported. Brady, Cohen, and Fischer[7] reported successful therapy with topical and systemic antibiotics for one patient with *P. acnes*. Tessler, Owens, and Deutsch[26] reported the approach of intracapsular injection of 0.2 ml of clindamycin (2 mg), which was performed on an outpatient basis every other day for a total of three treatments. The number of patients with *P. acnes* treated by these alternative techniques has been limited.

Based on our experience with these 19 patients, we recommend the following treatment approach in cases of delayed-onset pseudophakic endophthalmitis. In all cases, intraocular cultures should be performed, and pars plana vitrectomy is our preferred method for obtaining the specimen. We recommend a large central capsulectomy with selective removal of the area of white plaque at the time of the pars plana vitrectomy. Likewise, dense vitreous infiltrates should be removed during the pars plana vitrectomy. A more complete three-port pars plana vitrectomy is preferred if a satisfactory view of the posterior segment is possible. Intravitreal vancomycin hydrochloride, 1.0 mg, is our recommended antibiotic in patients with suspected bacterial infection, because vancomycin hydrochloride has been proven effective against *P. acnes* and *S. epidermidis* infections.[5,27] The *Corynebacterium* species isolates (Case 16) were also sensitive to vancomycin hydrochloride. Animal studies have shown that this dose of intravitreal vancomycin hydrochloride is well tolerated with no signs of retinal toxicity.[28] Although methicillin sodium and the cephalosporins may be effective, the increasing resistance of *S. epidermidis* to methicillin sodium gives vancomycin hydrochloride a distinct advantage in these cases.[29] Since *P. acnes* shows relative resistance to aminoglycoside antibiotics, we do not recommend the initial use of this class of antibiotics for suspected *P. acnes* endophthalmitis. The use of intraocular corticosteroids (dexamethasone, 0.4 mg) is optional but should be considered in eyes with more advanced inflammation.[30,31]

The role of intravenous antibiotic therapy in cases of endophthalmitis remains controversial. Brady, Cohen, and Fischer[7] described one patient with *P. acnes* endophthalmitis who was treated with prolonged intravenous, oral, and topical antibiotic therapy and regained 20/20 visual acuity. O'Day and associates[32] reported the successful use of subconjunctival, topical, and intravenous antibiotics without intravitreal antibiotics in patients with *S. epidermidis* endophthalmitis. However, subtherapeutic intravitreal concentrations of vancomycin hydrochloride were achieved in animal studies,[33,34] and systemic complications, such as periphlebitis, allergic reactions, and nephrotoxicity, have been reported in patients receiving intravenous vancomycin hydrochloride. Intravenous antibiotics were used during the brief hospital stay

of only one of our 19 patients with delayed-onset endophthalmitis (Case 1). Because of the retrospective nature of the present series without randomization of treatment, we are unable to draw any conclusions about the effectiveness of intravenous antibiotics in this category of endophthalmitis.

When characteristic stringy, white infiltrates are seen in the vitreous or cultures are positive for fungal elements, we recommend intravitreal injection of amphotericin B, 5 μg. Brod and associates[35] reported successful treatment of endogenous *Candida* species endophthalmitis without intravenous amphotericin B. To avoid the systemic toxicity associated with its use, systemic amphotericin B was not used in our patients with *Candida* species endophthalmitis. Treatment with oral imidazoles, such as ketoconazole or fluconazole, could be considered in patients with fungal infection.

The determination of a clinical cure was difficult in these patients with delayed-onset pseudophakic endophthalmitis because 12 patients had recurrence of marked inflammation and ten of these patients had positive culture results on repeat examination of intraocular fluids despite an apparent initial cure (Table 3). Nine patients required long-term use of topical corticosteroids postoperatively to suppress low-grade inflammation or episodes of acute-onset anterior uveitis. Despite these features, delayed-onset pseudophakic endophthalmitis has a more favorable visual prognosis, compared to other categories of endophthalmitis.

References

1. Ficker, L., Meredith, T. A., Wilson, L. A., Kaplan, H. J., and Kozarsky, A. M.: Chronic bacterial endophthalmitis. Am. J. Ophthalmol. 103:745, 1987.
2. Friedman, E., Peyman, G. A., and May, D. R.: Endophthalmitis caused by *Propionibacterium acnes*. Can. J. Ophthalmol. 13:50, 1978.
3. Meisler, D. M., Palestine, A. G., Vastine, D. W., Demartini, D. R., Murphy, B. F., Reinhart, W. J., Zakov, Z. N., McMahon, J. T., and Cliffel, T. P.: Chronic *Propionibacterium* endophthalmitis after extracapsular cataract extraction and intraocular lens implantation. Am. J. Ophthalmol. 102:733, 1986.
4. Jaffe, G. J., Whitcher, J. P., Biswell, R., and Irvine, A. R.: *Propionibacterium acnes* endophthalmitis seven months after extracapsular cataract extraction and intraocular lens implantation. Ophthalmic Surg. 17:791, 1986.
5. Zambrano, W., Flynn, H. W., Jr., Pflugfelder, S. C., Roussel, T. J., Culbertson, W. W., Holland, S., and Miller, D.: Management options for *Propionibacterium acnes* endophthalmitis. Ophthalmology 96:1100, 1989.
6. Roussel, T. J., Culbertson, W. W., and Jaffe, N. S.: Chronic postoperative endophthalmitis associated with *Propionibacterium acnes*. Arch. Ophthalmol. 105:1199, 1987.
7. Brady, S. E., Cohen, E. J., and Fischer, D. H.: Diagnosis and treatment of chronic postoperative bacterial endophthalmitis. Ophthalmic Surg. 19:580, 1988.
8. Forster, R. K., Abbott, R. L., and Gelender, H.: Management of infectious endophthalmitis. Ophthalmology 87:313, 1980.
9. Forster, R. K.: Etiology and diagnosis of bacterial postoperative endophthalmitis. Ophthalmology 85:320, 1978.
10. Forster, R. K., Zachary, I. G., Cottingham, A. J., Jr., and Norton, E. W. D.: Further observations on the diagnosis, cause, and treatment of endophthalmitis. Am. J. Ophthalmol. 81:52, 1976.
11. Walker, J., Dangel, M. E., Makley, T. A., and Opremcak, E. M.: Postoperative *Propionibacterium granulosum* endophthalmitis. Arch. Ophthalmol. 108:1073, 1990.
12. Seedor, J. A., Koplin, R. S., Shah, M., Almdeda, E. E., Jr., and Perry, H. D.: Chronic postoperative endophthalmitis from *Staphylococcus aureus*. J. Cataract Refract. Surg. 16:512, 1990.
13. Puliafito, C. A., Baker, A. S., Haaf, J., and Foster, C. S.: Infectious endophthalmitis. Review of 36 cases. Ophthalmology 89:921, 1982.
14. Stern, W. H., Tamura, E., Jacobs, R. A., Pons, V. G., Stone, R. D., O'Day, D. M., and Irvine, A. R.: Epidemic postsurgical *Candida parapsilosis* endophthalmitis, clinical findings and management of 15 consecutive cases. Ophthalmology 92:1701, 1985.
15. Pflugfelder, S. C., Flynn, H. W., Jr., Zwickey, T. A., Forster, R. K., Tsiligianni, A., Culbertson, W. W., and Mandelbaum, S.: Exogenous fungal endophthalmitis. Ophthalmology 95:19, 1988.
16. Roussel, T. J., Stern, W. H., Goodman, D. F., and Whitcher, J. P.: Postoperative mycobacterial endophthalmitis. Am. J. Ophthalmol. 107:403, 1989.
17. Driebe, W. T., Mandelbaum, S., Forster, R. K., Schwartz, L. K., and Culbertson, W. W.: Pseudophakic endophthalmitis. Diagnosis and management. Ophthalmology 93:442, 1986.
18. Olson, J. C., Flynn, H. W., Jr., Forster, R. K., and Culbertson, W. W.: Results in the treatment of postoperative endophthalmitis. Ophthalmology 90:692, 1983.
19. Semel, J., Nobe, J., Bowe, B., Finegold, S., and Smith, R. E.: *Propionibacterium acnes* isolated from explanted intraocular lens in pseudophakic bullous keratopathy. Cornea 8:259, 1989.
20. Rubinfeld, R. S., Cohen, E. J., Arentsen, J. J., and Laibson, P. R.: Diphtheroids as ocular pathogens. Am. J. Ophthalmol. 108:251, 1989.
21. McManaway, J. W., Weinberg, R. S., and Coudron, P. E.: *Coryneform* endophthalmitis. Two case reports. Arch. Ophthalmol. 108:942, 1990.

22. Mandelbaum, S., Forster, R. K., Gelender, H., and Culbertson, W. W.: Late onset endophthalmitis associated with filtering blebs. Ophthalmology 92:964, 1985.

23. Duker, J. S., and Belmont, J. B.: Late bacterial endophthalmitis following retinal detachment surgery. Retina 9:263, 1989.

24. Joondeph, B. C., Flynn, H. W., Jr., Miller, D., and Joondeph, H. C.: A new culture method for infectious endophthalmitis. Arch. Ophthalmol. 107:1334, 1989.

25. Stern, G. A., Engel, H. M., and Driebe, W. T., Jr.: Recurrent postoperative endophthalmitis. Cornea 9:102, 1990.

26. Tessler, H. H., Owens, S. L., and Deutsch, T. A.: Intracapsular bag diagnosis and treatment of *Propionibacterium acnes* endophthalmitis. Ophthalmology 96:118, 1989.

27. Smith, M. A., Sorenson, J. A., Lowy, F. D., Shakin, J. L., Harrison, W., and Jakobiec, F. A.: Treatment of experimental methicillin-resistant *Staphylococcus epidermidis* endophthalmitis with intravitreal vancomycin. Ophthalmology 93:1328, 1986.

28. Pflugfelder, S. C., Hernandez, E., Fliesler, S. J., Alvarez, J., Pflugfelder, M. E., and Forster, R. K.: Intravitreal vancomycin. Retinal toxicity, clearance, and interaction with gentamicin. Arch. Ophthalmol. 105:831, 1987.

29. Davis, J. L., Koidou Tsiligianni, A., Pflugfelder, S. C., Miller, D., Flynn, H. W., Jr., and Forster, R. K.: Coagulase negative staphylococcal endophthalmitis. Increase in antimicrobial resistance. Ophthalmology 95:1404, 1988.

30. Peyman, G. A., and Herbst, R.: Bacterial endophthalmitis. Treatment with intraocular injection of gentamicin and dexamethasone. Arch. Ophthalmol. 91:416, 1974.

31. Graham, R. O., and Peyman, G. A.: Intravitreal injection of dexamethasone. Treatment of experimentally induced endophthalmitis. Arch. Ophthalmol. 92:149, 1974.

32. O'Day, D. M., Jones, D. B., Patrinely, J., and Elliott, J. H.: *Staphylococcus epidermidis* endophthalmitis. Visual outcome following non-invasive therapy. Ophthalmology 89:354, 1982.

33. Pryor, J. G., Apt, L., and Leopold, I. H.: Intraocular penetration of vancomycin. Arch. Ophthalmol. 67:608, 1962.

34. Barza, M., Kane, A., and Baum, J.: Intraocular penetration of gentamicin after subconjunctival and retrobulbar injection. Am. J. Ophthalmol. 85:541, 1978.

35. Brod, R. D., Flynn, H. W., Jr., Clarkson, J. G., Pflugfelder, S. C., Culbertson, W. W., and Miller, D.: Endogenous *Candida* endophthalmitis management without intravenous amphotericin B. Ophthalmology 97:666, 1990.

OPHTHALMIC MINIATURE

After the war he intended to go back to London, where one could see one's own oculist. For Oliver's oculist had disappeared into the Army at the beginning of the war and he had chanced upon a very unlovable gentleman whose attitude towards his patients was that if his glasses did not suit them, something must be wrong with their eyes and it was entirely their own fault.

Angela Thirkell, *Marling Hall*
New York, Carroll & Graf Publishers, Inc., 1990, p. 66

Extracapsular Cataract Extraction With Intraocular Lens Implantation After Scleral Buckling Surgery

Richard S. Ruiz, M.D., and Osman A. Saatci, M.D.

We reviewed the records of 28 patients who had undergone successful scleral buckling surgery followed by extracapsular cataract extraction with implantation of an intraocular lens. Posterior chamber intraocular lenses were inserted in 27 eyes, and anterior chamber intraocular lenses were inserted in two eyes with posterior capsule rupture at the time of surgery. The mean follow-up period was 44 months. Final visual acuity was 20/40 or better in 15 of 29 eyes (52%). One eye (3.4%) developed a recurrent retinal detachment 15 months after cataract surgery. Two eyes (6.9%) developed angiographically proven cystoid macular edema. The outcome for extracapsular cataract extraction with intraocular lens implantation in eyes that had previously undergone successful scleral buckling for retinal detachment is favorable.

THE RATES OF REDETACHMENT after intracapsular cataract extraction in two studies reported by Ackerman and associates[1] in 1970 and by Pischel, Atkins, and Roth[2] in 1977 were 4% (three of 73 eyes) and 15.5% (nine of 58 eyes), respectively. Smiddy and associates[3] reported a recurrent retinal detachment rate of less than 3% in 31 eyes after standard extracapsular cataract extraction (ten with extracapsular cataract extraction alone and 21 with extracapsular cataract extraction and posterior chamber lens implantation). Smith and associates[4] emphasized that none of their 44 patients with pseudophakic retinal detachment of 3,065 total patients had previous retinal detachment surgery. We studied 29 eyes of 28 patients who had undergone extracapsular cataract extraction with intraocular lens implantation after successful scleral buckling surgery for retinal detachment.

Accepted for publication Nov. 2, 1990.

From the Department of Ophthalmology, Hermann Eye Center, University of Texas Medical School, Houston, Texas.

Reprint requests to Richard S. Ruiz, M.D., Hermann Eye Center, 6411 Fannin, 7th Fl., Houston, TX 77030.

Patients and Methods

We reviewed the records of 2,100 consecutive eyes that had undergone extracapsular cataract extraction with intraocular lens implantation between January 1981 and December 1989 to identify those eyes that had undergone previous successful scleral buckling surgery for retinal detachment. We excluded eyes that had a previous retinopexy without a scleral buckle, vitrectomy as part of the retinal detachment treatment, or diabetic retinopathy. Only those eyes with a minimum of six months of follow-up from the date of cataract surgery were included.

Information recorded before the cataract surgery included the following: age and sex of the patient; right or left eye; interval since retinal detachment repair; number of retinal detachment operations; visual acuity at the time of cataract surgery; optic disk and macular status of the involved eye; axial length of the 29 operated on eyes and 22 of the fellow eyes; and retinal status of the fellow eye.

Intraoperative complications were recorded, and postoperative data included the following: best-corrected visual acuity; subsequent YAG capsulotomy; duration of follow-up; and postoperative complications including retinal tears, retinal detachment, and cystoid macular edema.

Results

Age of the patients at the time of cataract surgery ranged from 38 to 83 years (mean, 66

years). Fourteen patients were men and 14 were women. There were 13 right eyes and 16 left eyes. The interval between previous retinal detachment repair and cataract surgery ranged from 18 to 280 months (mean, 137 months). Of 29 eyes, two (6.9%) had two scleral buckling procedures, and one (3.4%) had three scleral buckling procedures. The remaining 26 eyes (89.6%) had undergone one scleral buckling procedure. Best-corrected visual acuity before cataract surgery and best-corrected postoperative visual acuity are shown in the Figure.

Preoperatively, two eyes had age-related macular degeneration, two eyes had glaucomatous optic nerve damage, one eye had a preretinal membrane, and one eye had a macular hole.

Axial length measurements were performed before cataract surgery, and the mean axial length of the involved eyes was 25.63 mm. Of the 29 eyes, 17 (58.6%) had an axial length of 25.00 mm or longer. Nine of the 29 eyes (31%) had an axial length of 26.00 mm or longer. Axial length measurements were available in 22 fellow eyes; the mean was 25.22 mm. Seven of 22 fellow eyes (31.8%) had an axial length of longer than 25.00 mm.

Of 27 fellow eyes, 17 (63%) did not have retinal disease, and five (18.5%) had undergone previous retinal detachment repair. Five fellow eyes were treated with retinopexy because of tears or holes in the retina.

There were no modifications to our standard extracapsular cataract extraction technique. A limbal-based conjunctival flap and a 10-mm grooved incision were created. A large anterior capsulotomy was performed, and the nucleus was dislocated with an irrigating cannula and delivered with a lens loop. Posterior chamber intraocular lenses were placed in the ciliary sulcus in 27 of 29 eyes (93.1%). Two eyes (6.9%) received anterior chamber lenses because of rupture of the posterior capsule and vitreous loss. A meticulous anterior vitrectomy was performed to remove all vitreous from the incision and anterior chamber before anterior chamber lens insertion. No primary capsulotomies were performed. The incision was closed with six interrupted sutures.

Of 29 eyes, 15 (52%) attained visual acuity of 20/40 or better postoperatively, and 14 (48%) had final visual acuity of 20/50 or worse. In eight eyes with no preexisting conditions, visual acuity did not improve to better than 20/50. This was attributed to compromised retinal function because of involvement of the macula in the previous retinal detachment.

YAG capsulotomy was performed in six of 27 eyes (22.2%) from 19 to 77 months postoperatively. No recurrent retinal detachment was noted after posterior capsulotomy.

The follow-up period after cataract surgery varied from six to 104 months (mean, 44 months). There was a minimum follow-up period of 12 months in 25 of 29 eyes (86.2%).

Only one eye (3.4%) developed retinal detachment with a new retinal tear 15 months after the extracapsular cataract extraction with posterior chamber intraocular lens implantation with an intact posterior capsule. The retina was successfully attached by revising the scler-

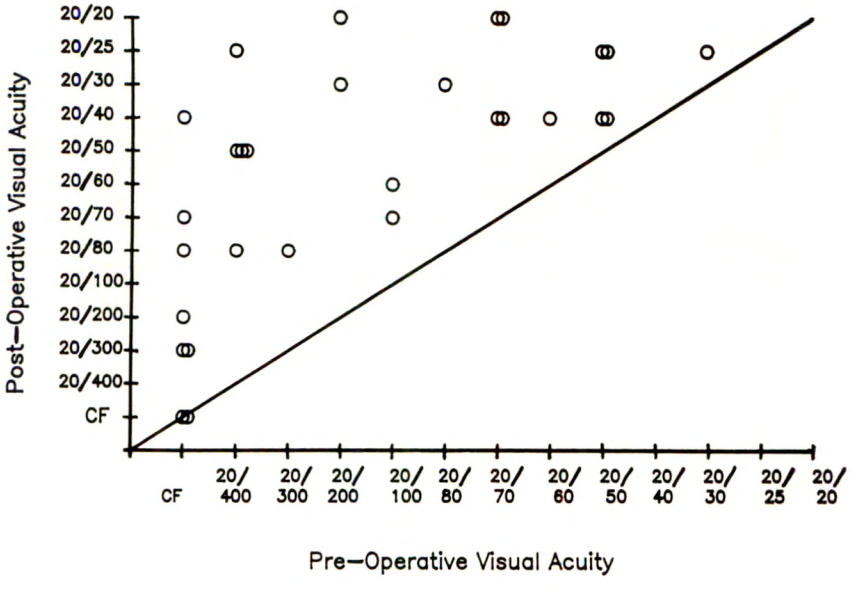


Figure (Ruiz and Saatci). Scattergram of best-corrected visual acuity before cataract surgery and best-corrected postoperative visual acuity. CF indicates counting fingers.

al buckle. Seventeen months later the retina detached again. A revision of the scleral buckle successfully reattached the retina with final visual acuity of 20/20. Twenty months after the second retinal detachment repair, YAG capsulotomy was performed with no change in retinal status. No other eyes developed retinal tears or detachments.

Two eyes (6.9%) developed angiographically proven cystoid macular edema. Both of these eyes attained a final visual acuity of 20/40.

Discussion

A family history of retinal detachment, previous retinal break or retinal detachment in either eye, lattice degeneration, and vitreous loss during cataract extraction were all considered as contraindications for intraocular lens implantation a decade ago.[5] Improved surgical techniques that maintain the integrity of the posterior capsule and the superior optical rehabilitation offered by intraocular lenses expanded the indications for intraocular lens implantation. We have performed extracapsular cataract extraction with posterior chamber intraocular lens implantation in patients after scleral buckling for previous retinal detachment. It is worthwhile to assess the outcome of extracapsular cataract extraction with intraocular lens implantation in this particular group of patients.

Smiddy and associates[3] found a recurrent retinal detachment rate of less than 3% after extracapsular cataract extraction with and without intraocular lens implantation in 31 eyes. Our redetachment rate of 3.4% (one of 29 eyes) is similar, but both series were small. The reported retinal detachment rates after extracapsular cataract extraction with or without intraocular lens implantation varies between 0.2% and 3.6%.[4,6-14] It is reported that 27% to 43%[4,13-17] of retinal detachments occur in the first six months and 46% to 74%[4,12-19] occur in the first 12 months after cataract surgery. Our mean follow-up period was 44 months with 86.2% of the patients (25 of 29 eyes) having 12 months or longer of follow-up.

High-risk factors predisposing to retinal detachment were prevalent in our patients. The average bilaterality rate for retinal detachment is 10%.[20] Five of 27 fellow eyes (18.5%) in our series had previous retinal detachment repair. Axial length of more than 25.00 mm is a risk factor for retinal detachment.[4,21] Patients with 25.00 mm or longer axial length had five times greater rate of retinal detachment according to Davison.[10] Armstrong and Lichenstein[22] reported a retinal detachment rate of 7.5% in 40 pseudophakic eyes, 38 of which had axial lengths of 25.00 mm or longer. Previous scleral buckling might have affected our axial length measurements. Although Kiernan, Leveille, and Morse[23] did not report any change in axial length in their patients, Larsen and Syrdalen[24] and Smiddy and associates[25] showed 0.98 to 0.99 mm of elongation after scleral buckling procedures. Of our 29 eyes, 17 (58.6%) had axial lengths of 25.00 mm or longer and nine (31%) had axial lengths of greater than 26.00 mm.

Vitreous loss at the time of cataract surgery increases the risk of retinal detachment.[26-28] When vitreous loss occurred, the retinal detachment incidence was 8.6% according to Coonan and associates.[12] In two of our cases, vitreous loss occurred without subsequent retinal detachment.

YAG capsulotomy is a possible risk factor.[29] Reported retinal detachment rates after YAG laser capsulotomy vary from 0.08% to 3.2%.[30-34] Coonan and associates[12] believe capsulotomy increases the retinal detachment rate threefold. In eyes with severe myopia, the risk is more significant.[33,35] In our study, six of 27 eyes (22.2%) received YAG capsulotomy, and no retinal detachment developed in these cases. The only eye with a recurrent retinal detachment in our series had laser capsulotomy after two scleral buckling operations without recurrence of the retinal detachment.

The amount of preserved macular function after retinal detachment was an important factor determining the ultimate visual outcome. Smiddy and associates[3] reported that five of 31 eyes (16%) did not attain 20/40 or better final visual acuity, although the eyes had clear optical media. Similarly, eight of our 29 eyes (27.6%) could not reach a level of 20/40 visual acuity without visibly apparent postoperative cause. Potential visual acuity meter or superpinhole testing preoperatively might yield valuable prognostic information about the macular status in this group of patients.

The visual outcome was affected in two eyes (6.9%) because of angiographically proven cystoid macular edema. The cystoid macular edema rate after extracapsular cataract extraction with intraocular lens implantation varies from 0.8%[8] to 7.1%.[19] Conversely, after retinal de-

tachment repair the prevalence of angiographic cystoid macular edema in phakic eyes has been reported to be 25% to 28%.[36-38] The cystoid macular edema rate in our patients was relatively high, and it might have been affected by the previous retinal detachment surgery.

The reattachment rate in pseudophakic eyes after retinal detachment repair is between 90% and 100%.[4,15-17,19,39] Pseudophakic retinal detachment associated with posterior chamber intraocular lens implantation has a more favorable anatomic and visual prognosis compared to anterior chamber or iris-fixated lenses.[40] Although our series of patients was small, the low recurrent retinal detachment rate of 3.4% in this group of 29 eyes of 28 patients with high-risk characteristics is encouraging. When performing extracapsular cataract extraction with intraocular lens implantation on patients considered to be at high risk for the development of retinal detachment, certain technical modifications are indicated. These include removal of all capsule anterior to the zonules and creation of an adequate pupillary aperture for improved visualization of the peripheral retina postoperatively. We believe that extracapsular cataract extraction with posterior chamber intraocular lens implantation is a safe technique for eyes with previous retinal detachment repair by scleral buckling.

References

1. Ackerman, A. L., Seelenfreund, M. H., Freeman, L. M., and Schepens, C. L.: Cataract extraction following retinal detachment surgery. Arch. Ophthalmol. 84:41, 1970.

2. Pischel, D. K., Atkins, R. E., and Roth, F. D.: Results in cataract extraction after retinal detachment surgery. Mod. Probl. Ophthalmol. 18:489, 1977.

3. Smiddy, W. E., Michels, R. G., Stark, W. J., and Maumenee, A. E.: Cataract extraction after retinal detachment surgery. Ophthalmology 95:3, 1988.

4. Smith, P. W., Stark, W. J., Maumenee, A. E., Enger, C. L., Michels, R. G., Glaser, B. M., and Bonham, R. D.: Retinal detachment after extracapsular cataract extraction with posterior chamber intraocular lens. Ophthalmology 94:495, 1987.

5. Freeman, H. M., Dobbie, J. G., Friedman, M. W., Johnston, G. P., Jungschaffer, O. H., McPherson, A. R., Nicholson, D. H., and Spalter, H. F.: Pseudophakic retinal detachment. Mod. Probl. Ophthalmol. 20:345, 1979.

6. Kratz, R. P.: Complications associated with posterior chamber lenses. Ophthalmology 86:659, 1979.

7. Laatikainen, L., and Tarkkanen, A.: Proliferative vitreoretinopathy after intraocular lens implantation. Acta Ophthalmol. 63:380, 1985.

8. Ridgway, A. E. A.: Discussion of factors responsible for retinal detachments and other late complications after intraocular lens implantation. Trans. Ophthalmol. Soc. U.K. 104:539, 1985.

9. Jaffe, N. S., Clayman, H. M., and Jaffe, M. S.: Retinal detachment in myopic eyes after intracapsular and extracapsular cataract extraction. Am. J. Ophthalmol. 97:48, 1984.

10. Davison, J. A.: Retinal tears and detachments after extracapsular cataract surgery. J. Cataract Refract. Surg. 14:624, 1988.

11. Gross, K. A., and Pearce, J. L.: Modern cataract surgery in a highly myopic population. Br. J. Ophthalmol. 71:215, 1987.

12. Coonan, P., Fung, W. E., Webster, R. G., Jr., Allen, A. W., and Abbott, R. L.: The incidence of retinal detachment following extracapsular cataract extraction. A ten-year study. Ophthalmology 92:1096, 1985.

13. Everett, W. G., Hurite, F. G., and Sorr, E. M.: Retinal detachment following cataract extraction by phacoemulsification. Mod. Probl. Ophthalmol. 18:503, 1977.

14. Wilkinson, C. P., Anderson, L. S., and Little, J. H.: Retinal detachment following phacoemulsification. Ophthalmology 85:151, 1978.

15. Wilkinson, C. P.: Pseudophakic retinal detachments. Retina 5:1, 1985.

16. Cousins, S., Boniuk, I., Okun, E., Johnston, G. P., Arribas, N. P., Escoffery, R. F., Burgess, D. B., Grand, M. G., Olk, R. J., and Schoch, L. H.: Pseudophakic retinal detachments in the presence of various intraocular lens types. Ophthalmology 93:1198, 1986.

17. Wilkinson, C. P.: Retinal detachment following intraocular lens implantation. Graefes Arch. Clin. Exp. Ophthalmol. 224:64, 1986.

18. Gray, R. H., Evans, A. R., Constable, I. J., and McAllister, I. L.: Retinal detachment and its relation to cataract surgery. Br. J. Ophthalmol. 73:775, 1989.

19. Ho, P. C., and Tolentino, F. I.: Pseudophakic retinal detachment. Surgical success rate with various types of intraocular lenses. Ophthalmology 91:847, 1984.

20. Benson, W. B.: Retinal Detachment. Diagnosis and Management, ed. 2. Philadelphia, J. B. Lippincott, 1988, p. 13.

21. Clayman, H. M., Jaffe, N. S., Light, D. S., Jaffe, M. S., and Cassady, J. C.: Intraocular lenses, axial length, and retinal detachment. Am. J. Ophthalmol. 92:778, 1981.

22. Armstrong, T. A., and Lichenstein, S. B.: Intraocular lenses in myopes. Ophthalmic Surg. 15:653, 1984.

23. Kiernan, J. P., Leveille, A. S., and Morse, P.: Axial length following scleral buckling. Retina 2:176, 1982.

24. Larsen, J. S., and Syrdalen, P.: Ultrasono-

graphic study on changes in axial eye dimension after encircling procedure in retinal detachment surgery. Acta Ophthalmol. 57:337, 1979.

25. Smiddy, W. E., Loupe, D. M., Michels, R. G., Enger, C., Glaser, B. M., and de Bustros, S.: Refractive changes after scleral buckling surgery. Arch. Ophthalmol. 107:1469, 1989.

26. Praeger, D. L.: Five years' follow-up in the surgical management of cataracts in high myopia treated with the Kelman phacoemulsification technique. Ophthalmology 86:2024, 1979.

27. Percival, S. P. B., Anand, V., and Das, S. K.: Prevalence of aphakic retinal detachment. Br. J. Ophthalmol. 67:43, 1983.

28. Wilkinson, C. P.: Retinal detachment after phacoemulsification. Am. J. Ophthalmol. 87:628, 1979.

29. Ober, R. R., Wilkinson, C. P., Fiore, J. V., Jr., and Maggiano, J. M.: Rhegmatogenous retinal detachment after neodymium:YAG laser capsulotomy in phakic and pseudophakic eyes. Am. J. Ophthalmol. 101:81, 1986.

30. Aron-Rosa, D. S., Aron, J. J., and Cohn, H. C.: Use of a pulsed picosecond Nd:YAG laser in 6,664 cases. Am. Intraocular Implant Soc. J. 10:35, 1984.

31. Keates, R. H., Steinert, R. F., Puliafito, C. A., and Maxwell, S. K.: Long-term follow-up of Nd:YAG laser posterior capsulotomy. Am. Intraocular Implant Soc. J. 10:164, 1984.

32. Johnson, S. H., Kratz, R. P., and Olson, P. F.: Clinical experience with the Nd:YAG laser. Am. Intraocular Implant Soc. J. 10:452, 1984.

33. Fickers, L. A., Vickers, S., Capon, M. R. C., Mellerio, J., and Cooling, R. J.: Retinal detachment following Nd:YAG posterior capsulotomy. Eye 1:86, 1987.

34. Seward, H. C., and Doran, R. M. L.: Posterior capsulotomy and retinal detachment following extracapsular lens surgery. Br. J. Ophthalmol. 68:379, 1984.

35. Percival, S. P. B.: Long-term complications from extracapsular cataract surgery. Trans. Ophthalmol. Soc. U.K. 104:915, 1985.

36. Meredith, T. A., Reeser, F. H., Topping, T. M., and Aaberg, T. M.: Cystoid macular edema after retinal detachment surgery. Ophthalmology 87:1090, 1980.

37. Miyake, K., Miyake, Y., Maekubo, K., Asakura, M., and Manabe, R.: Incidence of cystoid macular edema after retinal detachment surgery and the use of topical indomethacin. Am. J. Ophthalmol. 95:451, 1983.

38. Lobes, L. A., and Grand, G. M.: Incidence of cystoid macular edema following scleral buckling procedure. Arch. Ophthalmol. 98:1230, 1980.

39. Hagler, W. S.: Pseudophakic retinal detachment. Trans. Am. Ophthalmol. Soc. 80:45, 1982.

40. Isernhagen, R. D., and Wilkinson, C. P.: Visual acuity after the repair of pseudophakic retinal detachment involving the macula. Retina 9:15, 1989.

Quantitative Analysis of Lens Changes After Vitrectomy by Fluorophotometry

Yuichiro Ogura, M.D., Taiji Takanashi, M.D., Hitoshi Ishigooka, M.D., and Nobuchika Ogino, M.D.

We measured the amount of autofluorescence in the lens to evaluate quantitatively lens changes after vitrectomy. Thirteen phakic patients, ranging in age from 12 to 75 years, were studied after unilateral vitrectomy, with a follow-up period of more than two years (range, 26 to 55 months). Autofluorescence in the lens was measured at the center along the ocular axis by fluorophotometry. Lens autofluorescence in the eyes that underwent vitrectomy was significantly higher than in the contralateral eyes that were not operated on (P = .0003). The increase of autofluorescence was correlated significantly with the age at time of vitrectomy (P = .0008). There was no correlation between the increase in autofluorescence and the length of postoperative follow-up or the use of air during vitrectomy. Based on these results, we believe that oxidation of lens proteins intraoperatively may be one of the causes of development of nuclear cataract after vitrectomy.

NUCLEAR CATARACT has been shown to develop after pars plana vitrectomy, with a reported incidence from 13% to 79%.[1-5] Since eyes undergoing vitrectomy usually have complicated ocular diseases, such as vitreous hemorrhage, diabetic retinopathy, and uveitis, which themselves may cause lens changes, it is difficult to evaluate the association between vitrectomy and the postoperative cataractous changes. De Bustros and associates[4] reported that approximately half of the patients undergoing vitrectomy for removal of idiopathic epiretinal membrane subsequently showed development or progression of nuclear cataract. Because idiopathic epiretinal membranes are considered unrelated to cataract, the study confirmed a definite association between vitrectomy and the development of nuclear cataract.

Slit-lamp biomicroscopy was used to grade the lens changes in the study by de Bustros and associates[4] as well as in previous studies.[1-3] Slit-lamp examination is, however, subjective and does not give a quantitative measurement. Nuclear cataracts show a marked increase in light absorbance over a wide range of wavelengths, and there is a concomitant rise in long-wavelength fluorescence.[6] Studies have shown that fluorophotometric measurement of autofluorescence in the lens is useful to detect and quantitate the lens changes that occur in diabetes or with aging.[7-10] Using fluorophotometry, we measured the amount of autofluorescence in the lens of 13 patients after vitrectomy to evaluate the lens changes quantitatively.

Patients and Methods

Thirteen phakic patients were studied after vitrectomy, with a postoperative follow-up period of more than two years. All patients underwent unilateral vitrectomy at Kyoto University Hospital, Kyoto, Japan. They were informed about the purpose of the study, and their consent was obtained before initiation of the study. The patients ranged in age from 12 to 74 years (average, 51 years).

Nine patients required vitrectomy for removal of epiretinal membranes. The epiretinal membranes were of idiopathic cause in three eyes, subsequent to retinopexy and scleral buckling for primary rhegmatogenous retinal

Accepted for publication Oct. 16, 1990.

From the Department of Ophthalmology, Kyoto University, Kyoto, Japan (Drs. Ogura, Takanashi, and Ishigooka); and Department of Ophthalmology, Aichi Medical College, Aichi, Japan (Dr. Ogino). This study was supported in part by an International Research Scholar Award (Dr. Ogura) from Research to Prevent Blindness, Inc.

Reprint requests to Yuichiro Ogura, M.D., Applied Physics Laboratory, Department of Ophthalmology, College of Medicine, University of Illinois at Chicago, 1905 W. Taylor St., Chicago, IL 60612.

detachment in five eyes, and associated with trauma in one eye. Vitrectomy was performed in the other four patients to treat primary retinal detachment caused by a macular hole.

All procedures were performed by one of us (N.O.). Using local anesthesia, a three-port pars plana vitrectomy was performed. The conjunctiva was incised at the corneoscleral limbus to expose the sclera. Sclerotomies were made with a 19-gauge microvitreoretinal blade 4 mm from the corneoscleral limbus. A 4-mm infusion cannula was placed in the inferotemporal quadrant through the sclerotomy. Balanced salt solution prepared for ophthalmic surgery was used as an intraocular irrigating solution.[11] Epiretinal membranes were removed with a hooked 23-gauge disposable needle. An air-fluid exchange was performed on four patients with retinal detachment caused by macular hole. The retina remained attached after the operation in all patients, and no intraoperative or postoperative complications were observed.

Autofluorescence in the lens was measured by fluorophotometry. The average period between the operation and the fluorophotometric measurement was 38 ± 10 months (range, 26 to 55 months). The pupils were dilated with 1% tropicamide and 10% phenylephrine before the measurement. Patients with corneal or anterior chamber abnormalities, detected on slit-lamp examination, were excluded from the study. Patients with a focal lens opacity, which might interfere with the ability to perform fluorophotometric measurement, also were excluded.

Fluorophotometry was performed with a commercial computerized fluorophotometer. The main transmittance of the exciting filter was between 440 and 480 nm, and that of the barrier filter was between 530 and 630 nm. The instrument was described in detail previously.[12] Fluorescence of the lens was measured at the center along the ocular axis from the posterior capsule to the anterior capsule. Scans were performed with data points averaged for 100 milliseconds every 0.25 mm, and the results were expressed in equivalents to fluorescein sodium concentration (ng/ml Eq). The peak value was taken from a fluorophotometric profile and used for the analysis. Measurements were performed on both eyes, and the values in contralateral eyes, which did not undergo vitrectomy, were used for the control. It has been shown that amounts of lens autofluorescence measured by fluorophotometry are nearly equal in both eyes in healthy individuals.[10] The paired Student's *t*-test and the analysis of variance test were used for statistical evaluation.

Results

The values for autofluorescence of the central part of the lens as a function of age of the patients are shown for the treated and contralateral control eyes in Figure 1. Autofluorescence of the lens was correlated significantly with age both in treated eyes (r^2 = .87, P = .0001) and in control eyes (r^2 = .89, P = .0001). The autofluorescence increase in control eyes was comparable to that reported previously for normal individuals. Autofluorescence in the treated eyes was significantly higher than in the control eyes (P = .0003). When the difference between the treated and control eyes was plotted as a function of the age of patients, the increase of autofluorescence was significantly correlated with age at the time of the operation (r^2 = .65, P = .0008; Fig. 2). There was no correlation between the length of postoperative follow-up and the autofluorescence increase (r^2 = .02, P = .68).

An air-fluid exchange was performed in four patients with retinal detachment with macular hole. The mean increase of autofluorescence in these patients was compared with that in patients who did not receive air-fluid exchange at the time of the operation. The age was matched in the two groups. The fluorescence increase for eyes with air-fluid exchange was 98 ± 39 ng/ml Eq, whereas the fluorescence increase for eyes without air-fluid exchange was 110 ± 37 ng/ml Eq. No statistically significant difference was found between the two groups (P = .67).

Discussion

In the human lens, two major types of fluorescence are detected, one of which is emitted around 340 nm when excited at 290 nm (purple fluorescence), and the other with excitation and emission wavelengths of approximately 340 and 420 nm, respectively (blue fluorescence). Satoh, Bando, and Nakajima[13] reported that the purple fluorescence of the human lens is maintained at a relatively constant level throughout life, whereas the blue fluorescence increases with age. Jacobs and Krohn[14] showed that the fluorescence measured at 530 nm, which is similar to the wavelength used in our study, increases with age, especially in the nuclear region. The long-wavelength fluorescence has been suggested to originate oxidation products of tryptophan in the lens.[15] Previous studies

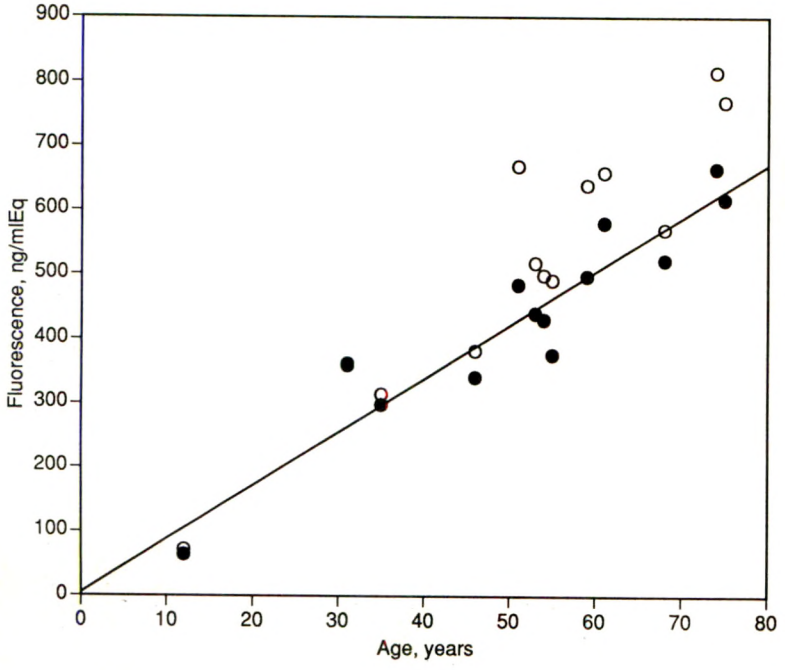


Fig. 1 (Ogura and associates). Fluorescence in the lens as a function of age of the patients at time of vitrectomy. Open circles indicate the results from the eyes that underwent vitrectomy; closed circles indicate the results from the untreated contralateral eyes; and the line indicates the regression line for the control eyes.

using the same type of fluorophotometer as in our study have shown that this technique is useful to quantitate the increase in fluorescence in the lens that occurs with aging or diabetes mellitus.[7,10] Our results indicate that vitreous surgery also causes an accumulation of fluorescent materials in the lens. Nine patients in this study had retinal detachment before or at the time of vitrectomy, which may influence the lens changes. Mandai and associates,[16] however, confirmed that autofluorescence in the lens did not increase after retinal detachment and treatment with scleral buckling.

The increase in the lens autofluorescence was correlated significantly with age of the patients at the time of the operation. This finding suggested that lenses of older patients are more vulnerable to lens changes after surgical intervention than are lenses of younger patients. De Bustros and associates[4] also noted that younger patients had a lower incidence of postoperative nuclear sclerosis, although this difference was

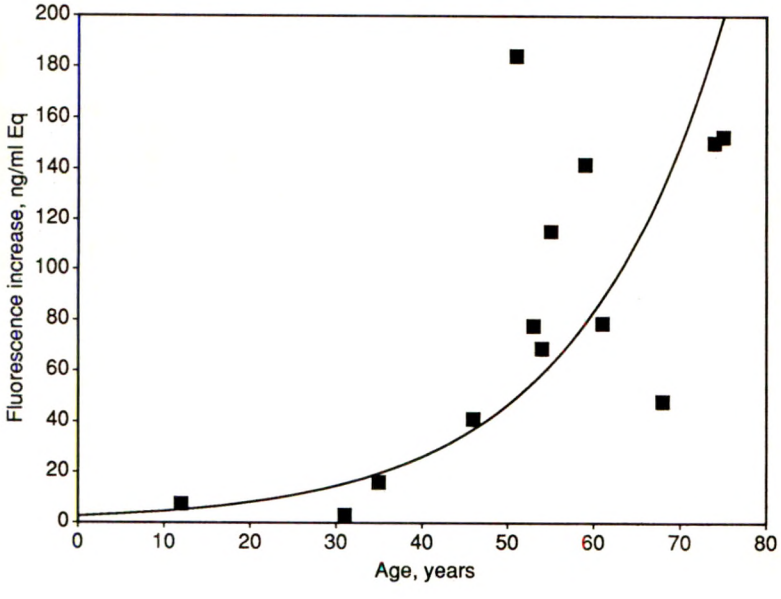


Fig. 2 (Ogura and associates). Increase of fluorescence in the treated eyes as a function of age of the patients at time of vitrectomy. The fluorescence increase was calculated by subtracting the value in the contralateral eye from the value in the eye that underwent vitrectomy.

not statistically significant. The potential for postoperative progression of cataract should be kept in mind when vitrectomy is performed on patients older than 50 years of age.

We did not find a relationship between the length of postoperative follow-up and the lens changes. This may be because of the small population of patients in our study or because we enrolled only the patients with postoperative follow-up periods of more than 24 months, since the purpose of the study was to demonstrate late changes of the lens. Poliner and associates[3] reported that cataractous progression was observed in 48% of patients at 12 months and in 68% at 24 months after vitrectomy for premacular fibroplasia. The preliminary results of the study of Ogino, Kitagawa, and Ogura[17] suggested that the lens changes start within six months after surgery and deteriorate gradually thereafter.

It has been known that prolonged intravitreal gas tamponade using long-acting gases such as perfluoropropane or sulfur hexafluoride sometimes causes posterior subcapsular opacities from a direct contact with the posterior surface of the lens and gas bubbles.[18,19] Our results, however, suggested that gas tamponade with air does not influence the late changes of the lens fluorescence after vitrectomy. The effects of long-acting gases still remain to be determined.

Nuclear sclerosis is known to develop with aging. It has been suggested that nuclear sclerosis is caused by extensive crosslinking of the lens proteins and that one type of the major crosslinks is disulfide crosslink, which results from oxidation of protein sulfhydryl groups, although the origin of the oxidative insult is unknown.[6] It also has been shown that prolonged hyperbaric oxygen treatment causes nuclear sclerosis of the lens, especially in elderly patients.[20,21] From these results it is possible that oxygen plays an important role in the development of nuclear sclerosis. Oxygen tension in the aqueous humor is reported to be 30 to 40 mm Hg at the mid anterior chamber.[22,23] Sakaue, Negi, and Honda[24] measured oxygen tension in the human vitreous before vitreous surgery. According to their study, the average oxygen tension in the anterior vitreous was 16.7 ± 3.7 mm Hg. These results suggested that the lens environment is usually relatively low in oxygen. Considering that the irrigating solution is equilibrated with air at an atmospheric pressure, oxygen tension in the irrigating solution is estimated to be approximately 150 mm Hg (20% of 760 mm Hg). Therefore, the lens is exposed to an extremely high level of oxygen, five to ten times higher than normal, during vitreous surgery. It is reasonable to speculate that a high concentration of oxygen in the irrigating solution contributes to oxidation of proteins in the lens, which later may lead to an increase of fluorescent derivatives and development of nuclear cataract.

Additionally, intensive light exposure from an operating microscope may be a facilitating factor for the oxidation of lens proteins. Mitchell and Anderson[25] reported that catalase, which is one of the antioxidant enzymes existing in the lens, is inactivated in the presence of oxygen and light. Inactivation of antioxidant enzymes in the lens by light from the operating microscope may further promote oxidation of the lens proteins. It has been reported that the activity of antioxidative enzymes in the human lens, such as superoxide dismutase and glutathione peroxidase, decreases with age and at the onset of nuclear sclerosis.[26] This may explain the results of our study and the development of nuclear sclerosis after hyperbaric oxygen treatment,[20] both of which demonstrated the vulnerability of lenses of older patients to posttreatment lens changes.

Measurement of fluorescence in the lens is useful to detect and quantitate the changes that occur after vitrectomy. Moreover, quantitative analysis demonstrated that older lenses are more susceptible to lens changes after surgical intervention, which suggests that oxidation of lens proteins during vitrectomy may be one of the causes of development of nuclear cataract after this procedure.

References

1. Margherio, R. R., Cox, M. S., Trese, M. T., Murphy, P. L., Johnson, J., and Minor, L. A.: Removal of epimacular membranes. Ophthalmology 92:1075, 1985.

2. McDonald, H. R., Verre, W. P., and Aaberg, T. M.: Surgical management of idiopathic epiretinal membranes. Ophthalmology 93:978, 1986.

3. Poliner, L. S., Olk, R. J., Grand, G., Escoffery, R. F., Okun, E., Boniuk, I., and Farber, M. J.: Surgical management of premacular fibrosis. Arch. Ophthalmol. 106:761, 1988.

4. de Bustros, S., Thompson, J. T., Michels, R. G., Enger, C. L., Rice, T. A., and Glaser, B. M.: Nuclear sclerosis after vitrectomy for idiopathic epiretinal membranes. Am. J. Ophthalmol. 105:160, 1988.

5. Dobbs, R. E., Lambrou, F., Bates, S., Aaberg, T. M., Edelhauser, H. F., Laser, H., Eckerskorn, U., and Hockwin, O.: Quantitation of lens clarity changes in idiopathic epiretinal membrane surgery patients. In de Oliveira, F. (ed.): Ophthalmology Today. Amsterdam, Elsevier Science Publishers, 1988, pp. 507–508.

6. Cotlier, E.: The lens. In Moses, R. A., and Hart, W. M., Jr. (eds.): Adler's Physiology of the Eye. Clinical Application. St. Louis, C. V. Mosby, 1987, pp. 268–290.

7. Zeimer, R. C., and Noth, J. M.: A new method of measuring in vivo the lens transmission, and study of lens scatter, fluorescence and transmittance. Invest. Ophthalmol. Vis. Sci. 16:246, 1984.

8. van Best, J. A., Tjin, A., Tsoi, E. W. S. J., Boot, J. P., and Oosterhuis, J. A.: In vivo assessment of lens transmission for blue-green light by autofluorescence measurements. Ophthalmic Res. 17:90, 1985.

9. van Best, J. A., Vrij, L., and Oosterhuis, J. A.: Lens transmission of the blue-green light in diabetes measured by autofluorophotometry. Invest. Ophthalmol. Vis. Sci. 26:532, 1985.

10. Bleeker, J. C., van Best, J. A., Vrij, L., van der Velde, E. A., and Oosterhuis, J. A.: Autofluorescence of the lens in diabetic and healthy subjects by fluorophotometry. Invest. Ophthalmol. Vis. Sci. 27:791, 1986.

11. Negi, A., Honda, Y., and Kawano, S.-I.: Effects of intraocular irrigating solutions on the electroretinographic b-wave. Am. J. Ophthalmol. 92:28, 1981.

12. Zeimer, R. C., Blair, N. P., and Cunha-Vaz, J. G.: Vitreous fluorophotometry for clinical research. I. Description and evaluation of a new fluorophotometer. Arch. Ophthalmol. 101:1753, 1983.

13. Satoh, K., Bando, M., and Nakajima, A: Fluorescence in human lens. Exp. Eye Res. 16:167, 1973.

14. Jacobs, R., and Krohn, D. L.: Fluorescence intensity profile of human lens. Invest. Ophthalmol. Vis. Sci. 20:117, 1981.

15. Kurzel, R. B., Wolbarsht, M. L., and Yamanishi, B. S.: Spectral studies on normal and cataractous intact human lens. Exp. Eye Res. 17:65, 1973.

16. Mandai, M., Tanihara, H., Ogura, Y., Kawano, S., Ohuchi, T., and Ogino, N.: Autofluorescence in the lens after retinal detachment surgery. Jpn. J. Clin. Ophthalmol. 44:518, 1990.

17. Ogino, N., Kitagawa, K., and Ogura, Y.: Progression of nuclear cataract after retinal surgery. J. Eye 6:1592, 1989.

18. Fineberg, E., Machemer, R., Sullivan, P., Norton, E. W. D., Hamasaki, D., and Anderson, D.: Sulfur hexafluoride in owl monkey vitreous cavity. Am. J. Ophthalmol. 79:67, 1975.

19. Lincoff, H., Mardirossian, J., Lincoff, A., Liggett, P., Iwamoto, T., and Jakobiec, F.: Intravitreal longevity of three perfluorocarbon gases. Arch. Ophthalmol. 98:1610, 1980.

20. Schocket, S. S., Esterson, J., Bradford, B., Michaelis, M., and Richards, R. D.: Induction of cataracts in mice by exposure to oxygen. Isr. J. Med. Sci. 8:1596, 1972.

21. Palmquist, B.-M., Philipson, B., and Barr, P.-O.: Nuclear cataract and myopia during hyperbaric oxygen therapy. Br. J. Ophthalmol. 68:113, 1984.

22. Stefansson, E., Wolbarsht, M. L., and Landers, M. B.: The corneal contact lens and aqueous humor hypoxia in cats. Invest. Ophthalmol. Vis. Sci. 24:1052, 1983.

23. Stefansson, E., Robinson, D., Wolbarsht, M. L., Landers, M. B., and Walsh, A.: Effect of epinephrine on PO_2 in anterior chamber. Arch. Ophthalmol. 101:636, 1983.

24. Sakaue, H., Negi, A., and Honda, Y.: Comparative study of vitreous oxygen tension in human and rabbit eyes. Invest. Ophthalmol. Vis. Sci. 30:1933, 1989.

25. Mitchell, R. L., and Anderson, I. C.: Catalase photoinactivation. Science 150:74, 1965.

26. Fecondo, J. V., Augusteyn, R. C.: Superoxide dismutase, catalase and glutathione peroxidase in the human cataractous lens. Exp. Eye Res. 36:15, 1983.

Control of Intraocular Pressure With Apraclonidine Hydrochloride After Cataract Extraction

Stephen B. Wiles, M.D., Douglas MacKenzie, M.D., and Carl H. Ide, M.D.

We conducted a randomly assigned, double-masked, controlled clinical trial to assess the efficacy of 1% apraclonidine hydrochloride in controlling postoperative intraocular pressure increases in patients undergoing extracapsular cataract extraction. Apraclonidine hydrochloride was given either one hour preoperatively or immediately after uncomplicated, extracapsular cataract extraction with posterior chamber intraocular lens implantation and compared with artificial tears given immediately postoperatively. Those who received apraclonidine hydrochloride preoperatively had significantly lower mean intraocular pressure at the first postoperative reading (P = .0005). After preoperative and postoperative apraclonidine hydrochloride, the mean early postoperative intraocular pressure was 19.8 mm Hg and 32.0 mm Hg, respectively, and 27.6 mm Hg after artificial tears. No patient who received preoperative apraclonidine hydrochloride had an intraocular pressure increase to 30 mm Hg or higher postoperatively. Nine of 20 patients (45%) who received postoperative apraclonidine hydrochloride and eight of 18 patients (44%) who received postoperative artificial tears had an increase of intraocular pressure to 30 mm Hg or higher in the early postoperative period. These differences were also highly significant (P = .0005).

Accepted for publication Oct. 25, 1990.

From the University of Missouri-Columbia, Mason Institute of Ophthalmology, and the Harry S Truman Memorial Veterans Administration Hospital, Columbia, Missouri. This study was presented at the spring meeting of the Missouri Ophthalmological Society, Inc., Lake Ozark, Missouri, April 7, 1990. This study was supported in part by a grant from Research to Prevent Blindness, Inc.

Reprint requests to Stephen B. Wiles, M.D., University of Missouri-Columbia, Mason Institute of Ophthalmology, One Hospital Dr., Columbia, MO 65212.

INTRAOCULAR PRESSURE INCREASES after cataract extraction have been well described.[1-4] A variety of mechanisms have been postulated to account for this phenomenon, and the use of some agents, such as viscoelastics, has been associated with higher postoperative intraocular pressure.[5] Sudden and profound increases in intraocular pressure can be hazardous to visual outcome, especially in patients with pre-existing compromised optic nerves or vasculature. Many agents have been studied to determine their effect on intraocular pressure in the postoperative period after cataract extraction. These include beta-blockers, miotics, carbonic anhydrase inhibitors, viscoelastics, and alpha-chymotrypsin. One study found that timolol maleate given both preoperatively and postoperatively in each patient reduced postoperative intraocular pressure increases in patients undergoing intracapsular cataract extraction without alpha-chymotrypsin.[2] Another group found that timolol maleate given only postoperatively had minimal effect on reducing intraocular pressure after cataract extraction.[3] Other medications can prevent postoperative intraocular pressure increases when given postoperatively.[6-9] The ability of an aqueous suppressant to influence the postoperative intraocular pressure may depend in part on the time of application. Apraclonidine hydrochloride is a relatively new ocular hypotensive agent whose effect on intraocular pressure after cataract surgery is not known. Intraocular pressure increases after argon laser trabeculoplasty, argon laser iridotomy, and YAG posterior capsulotomy can be prevented in many patients by pretreating with apraclonidine hydrochloride. We conducted a randomly assigned, double-masked, controlled clinical trial to determine the effect of 1% apraclonidine hydrochloride, given either preoperatively or postoperatively, on postoperative intraocular pressure in patients undergoing uncomplicated extracapsular cataract extraction.

Patients and Methods

Sixty-five patients scheduled for extracapsular cataract extraction were randomly assigned to one of three groups: preoperative apraclonidine hydrochloride, postoperative apraclonidine hydrochloride, or postoperative artificial tears. Patients were excluded from consideration for the following reasons: if they had a history of uveitis, glaucoma, or previous ocular surgery; preoperative intraocular pressure of 22 mm Hg or above; if they were taking topical ocular medications chronically; or if they had a contraindication to posterior chamber intraocular lens implantation. One patient with scleroderma was also excluded. We analyzed a total of 57 patients who met these criteria. One patient from the preoperative apraclonidine hydrochloride group, four patients from the postoperative apraclonidine hydrochloride group, and two patients from the artificial tear group were being treated with systemic beta-blockers.

Of the 19 men in the preoperative apraclonidine hydrochloride group, the mean age was 64.6 years (range, 49 to 80 years). Five right eyes and 14 left eyes were affected.

Of the 20 men in the postoperative apraclonidine hydrochloride group, the mean age was 70.7 years (range, 43 to 89 years). Eleven right eyes and nine left eyes were affected.

Of the 18 men in the artificial tear group, the mean age was 69.2 years (range, 48 to 79 years). Ten right eyes and eight left eyes were affected.

All patients underwent extracapsular cataract extraction and implantation of a 7.0-mm posterior chamber intraocular lens. Informed consent was obtained from every patient. Pupils were dilated preoperatively with three sets of one drop each of 2.5% phenylephrine hydrochloride and 1% cyclopentolate hydrochloride, five minutes apart. Noncorticosteroidal antiinflammatory preparations were not given to any patient. Nineteen patients received two drops of 1% apraclonidine hydrochloride one hour before surgery. Each patient received local anesthesia using a modified O'Brien or van Lint facial nerve block (5.0 ± 1.0 ml) and retrobulbar block (3.0 ± 1.0 ml) with an equal mixture of 2% lidocaine with epinephrine and 0.75% bupivacaine hydrochloride with hyaluronidase. Digital pressure was applied until intraocular pressure by Schiötz tonometry was less than 10 mm Hg. A standard extracapsular procedure was performed using an irrigating solution containing epinephrine (1.0 ml of 1:1,000 dilution added to 500 ml of balanced salt solution) to enhance pupillary dilation during removal of the cortex. Intracameral sodium hyaluronate was used before anterior capsulotomy and intraocular lens placement and was aspirated before final closure of the incision. Intracameral 1% acetylcholine chloride (0.5 ± 0.25 ml) was given to promote miosis. In every patient watertight incision closure was performed with seven to ten interrupted 10-0 nylon sutures. Subconjunctival gentamicin sulfate (0.5 ml) and betamethasone (0.5 ml) were injected at the end of the procedure. Before patching, 20 patients received two drops of apraclonidine hydrochloride, and 18 patients received two drops of artificial tears.

Having no knowledge of which type of eyedrop the patient received, the surgeon determined the end point of intraocular pressure measurement by applanation tonometry, using the same Goldmann applanation tonometer, for a particular patient at each time interval. Another investigator observed the tonometer scale value and recorded this number without informing the surgeon of the reading. Horizontal and vertical values were averaged to minimize the effect of astigmatism on readings. Measurements were taken 12 hours preoperatively, five to eight hours postoperatively (early), and 24 hours postoperatively (late).

Any patient in whom intraocular pressure reached 30 mm Hg or higher in the early postoperative period received additional treatment with a topical beta-blocker, oral acetazolamide, or both, depending on the severity of the increase. Supplemental intraocular pressure readings were taken when appropriate to ensure that all patients received adequate intraocular pressure control after the operation.

Results

Kruskall-Wallis analysis of variance and Duncan's multiple range testing were used to analyze mean intraocular pressure differences. Preoperative intraocular pressure was not significantly different between groups (preoperative apraclonidine hydrochloride group, 14.4 ± 2.5 mm Hg; postoperative apraclonidine hydrochloride group, 15.7 ± 2.4 mm Hg; artificial tear group, 14.9 ± 2.8 mm Hg). Preoperative intraocular pressure was not significantly different between patients who were receiving

systemic beta-blockers and those who were not. Mean intraocular pressure at the early postoperative visit was significantly lower in patients pretreated with apraclonidine hydrochloride (19.8 ± 4.9 mm Hg) when compared to those receiving either apraclonidine hydrochloride postoperatively (32.0 ± 11.4 mm Hg) or artificial tears (27.6 ± 8.3 mm Hg) (P = .002). Mean change from preoperative intraocular pressure at the early postoperative measurement was +5.4 mm Hg in the pretreated group (P = .002), +16.3 mm Hg in the postoperative apraclonidine hydrochloride group (P = .0001), and +12.7 mm Hg in the artificial tear group (P = .0006). A significantly smaller mean pressure increase at the early postoperative visit was observed in the preoperative apraclonidine hydrochloride group when compared with the other groups (P = .0005). The difference in pressure increase between the postoperative apraclonidine hydrochloride and artificial tear groups was not significantly different.

No patient who received apraclonidine hydrochloride preoperatively had an increase in intraocular pressure to 30 mm Hg or above postoperatively. Of the 20 patients who received apraclonidine hydrochloride postoperatively, nine (45%) had an early postoperative pressure increase to 30 mm Hg or above, and of the 18 patients who received artificial tears, eight (44%) had such an increase. Chi-square analysis of proportions showed these differences to be highly significant (P = .002). Comparisons between groups indicated no difference between the postoperative apraclonidine hydrochloride and artificial tear groups in the proportion of patients with intraocular pressure increases to 30 mm Hg or higher postoperatively. Four of 19 patients (21%) in the preoperative apraclonidine hydrochloride group, 13 of 20 patients (65%) in the postoperative apraclonidine hydrochloride group, and 12 of 18 patients (67%) in the artificial tear group had an intraocular pressure increase of 10 mm Hg or more at the first postoperative visit.

All patients with postoperative intraocular pressure of 30 mm Hg or higher were treated with adjunctive medical treatment, and in every patient, intraocular pressure was successfully decreased to an adequate level at the late postoperative intraocular pressure reading. None of the patients who received preoperative apraclonidine hydrochloride required adjunctive treatment, and mean postoperative intraocular pressure at 24 hours was 16.7 ± 5.9 mm Hg for this group. This was not significantly different from preoperative readings. For patients not requiring adjunctive medication in the other groups, there was no significant difference in late postoperative pressure from baseline. The mean late postoperative intraocular pressure at 24 hours was 17.0 ± 3.9 mm Hg in the postoperative apraclonidine hydrochloride group and 17.9 ± 2.4 mm Hg in the artificial tear group. No patient whose initial postoperative reading was below 30 mm Hg had an increase in intraocular pressure to this level at 24 hours. The highest intraocular pressure recorded at the early postoperative reading for patients receiving preoperative apraclonidine hydrochloride was 24 mm Hg.

Postoperative inflammation did not correlate with intraocular pressure in any group. There were no complications of treatment observed.

Discussion

Apraclonidine hydrochloride is a relatively selective alpha-2 agonist. This drug works peripherally and has limited access to the central nervous system. Topical application results in peripheral nonselective alpha agonistic properties, such as unilateral transient eyelid retraction, conjunctival blanching, and xerostomia.[10] Serdahl, Galustian, and Lewis[11] demonstrated a reduction in conjunctival oxygen tension after topical administration. No significant changes in blood pressure or heart rate have been found.[12-16]

Apraclonidine hydrochloride has a peak effect at two to five hours after administration and a duration of approximately 12 hours. It reduces intraocular pressure in normal and glaucomatous eyes.[12-14,17] Abrams and associates[14] found a maximum mean decrease of 3.6 mm Hg and 3.0 mm Hg at two and 12 hours, respectively, after treatment in normal eyes when diurnal fluctuations in intraocular pressure were considered. Similarly, in glaucomatous eyes, a decrease of 4.7 mm Hg and 3.1 mm Hg, at two and 12 hours respectively, occurred. Tachyphylaxis did not develop after prolonged treatment. Jampel and associates[12] suggested that lower concentrations may be as effective as the 1% solution. A small but significant reduction in intraocular pressure in the contralateral eye may occur.[10]

Apraclonidine hydrochloride reduces intraocular pressure by inhibiting aqueous humor production, by up to 35%, as shown by fluoro-

photometry.[17] The effect of apraclonidine hydrochloride on uveoscleral outflow is not known, and there appears to be no effect on outflow facility in humans.[10] When given preoperatively, apraclonidine hydrochloride is effective in limiting the increase in intraocular pressure after argon laser trabeculoplasty,[15,18,19] argon laser iridotomy,[15,19,20] and YAG posterior capsulotomy.[15,19,21]

Our results show that mean postoperative intraocular pressure between five and eight hours after surgery is significantly lower in patients who received apraclonidine hydrochloride preoperatively. All groups had a mean increase in intraocular pressure at the early postoperative reading. Mean change in intraocular pressure at the first postoperative visit was significantly lower after pretreatment with apraclonidine hydrochloride (+5.4 mm Hg) when compared with postoperative apraclonidine hydrochloride (+16.3 mm Hg) or artificial tears (+12.7 mm Hg). None of the patients who received apraclonidine hydrochloride preoperatively had a postoperative increase in intraocular pressure to 30 mm Hg or higher. This was significantly lower than the number of patients who had an intraocular pressure increase to 30 mm Hg or higher after postoperative apraclonidine hydrochloride (nine of 20 patients [45%]) or artificial tears (eight of 18 patients [44%]).

The ineffectiveness of immediate postoperative treatment with apraclonidine hydrochloride suggests that surgical trauma preempts the intraocular pressure lowering effect of apraclonidine hydrochloride. Preoperative apraclonidine hydrochloride may stabilize the ciliary structure such that it responds poorly to mediators released in response to surgery. Ciliary stabilization preoperatively, possibly vascular or epithelial, appears to be necessary for early postoperative intraocular pressure to be controlled by apraclonidine hydrochloride.

Flurbiprofen, a noncorticosteroidal antiinflammatory drug, is used to inhibit intraoperative miosis during cataract surgery. This agent was not used in our study since its effect on prostaglandin liberation might have influenced the intraocular pressure after surgery. Additionally, there are opposing views about the relationship between apraclonidine hydrochloride and flurbiprofen.[22,23]

Our data suggest that apraclonidine hydrochloride given preoperatively minimizes the postoperative intraocular pressure increase observed after extracapsular cataract extraction. Surgeons should consider preoperative apraclonidine hydrochloride for those patients at risk for visual loss from high postoperative intraocular pressure.

References

1. Rich, W. J., Radtke, N. D., and Cohan, B. E.: Early ocular hypertension after cataract extraction. Br. J. Ophthalmol. 58:725, 1974.
2. Haimann, M. H., and Phelps, C. D.: Prophylactic timolol for the prevention of high intraocular pressure after cataract extraction. Ophthalmology 88:233, 1981.
3. Ruiz, R. S., Wilson, C. A., Musgrove, K. H., and Prager, T. C.: Management of increased intraocular pressure after cataract extraction. Am. J. Ophthalmol. 103:487, 1987.
4. Savage, J. A., Thomas, J. V., Belcher, C. D., III, and Simmons, R. J.: Extracapsular cataract extraction and posterior chamber intraocular lens implantation in glaucomatous eyes. Ophthalmology 92:1506, 1985.
5. Glasser, D. B., Matsuda, M., and Edelhauser, H. F.: A comparison of the efficacy and toxicity of and intraocular pressure response to viscous solutions in the anterior chamber. Arch. Ophthalmol. 104:1819, 1986.
6. West, D. R., Lischwe, T. D., Thompson, V. M., and Ide, C. H.: Comparative efficacy of the beta-blockers for the prevention of increased intraocular pressure after cataract extraction. Am. J. Ophthalmol. 106:168, 1988.
7. Hollands, R. H., Drance, S. M., and Schulzer, M.: The effect of acetylcholine on early postoperative intraocular pressure. Am. J. Ophthalmol. 103:749, 1987.
8. ———: The effect of intracameral carbachol on intraocular pressure after cataract extraction. Am. J. Ophthalmol. 104:225, 1987.
9. Ruiz, R. S., Rhem, M. N., and Prager, T. C.: Effects of carbachol and acetylcholine on intraocular pressure after cataract extraction. Am. J. Ophthalmol. 107:7, 1989.
10. Robin, A. L.: Short-term effects of unilateral 1% apraclonidine therapy. Arch. Ophthalmol. 106:912, 1988.
11. Serdahl, C. L., Galustian, J., and Lewis, R. A.: The effects of apraclonidine on conjunctival oxygen tension. Arch. Ophthalmol. 107:1777, 1989.
12. Jampel, H. D., Robin, A. L., Quigley, H. A., and Pollack, I. P.: Apraclonidine. A one-week dose-response study. Arch. Ophthalmol. 106:1069, 1988.
13. Abrams, D. A., Robin, A. L., and Pollack, I. P.: The safety and efficacy of topical 1% ALO 2145 (p-aminoclonidine hydrochloride) in normal volunteers. Arch. Ophthalmol. 105:1205, 1987.
14. Abrams, D. A., Robin, A. L., Crandall, A. S., Caldwell, D. R., Schnitzer, D. B., Pollack, I. P.,

Rader, J. E., and Reaves, T. A., Jr.: A limited comparison of apraclonidine's dose response in subjects with normal or increased intraocular pressure. Am. J. Ophthalmol. 108:230, 1989.

15. Robin, A. L.: The role of apraclonidine hydrochloride in laser therapy for glaucoma. Trans. Am. Ophthalmol. Soc. 87:729, 1989.

16. Coleman, A. L., Robin, A. L., Pollack, I. P., Rudikoff, M. T., Enger, C., and Mayer, P. R.: Cardiovascular and intraocular pressure effects and plasma concentrations of apraclonidine. Arch. Ophthalmol. 108:1264, 1990.

17. Gharagozloo, N. Z., Relf, S. J., and Brubaker, R. F.: Aqueous flow is reduced by the alpha-adrenergic agonist, apraclonidine hydrochloride (ALO 2145). Ophthalmology 95:1217, 1988.

18. Robin, A. L., Pollack, I. P., House, B., and Enger, C.: Effects of ALO 2145 on intraocular pressure following argon laser trabeculoplasty. Arch. Ophthalmol. 105:646, 1987.

19. Brown, R. H., Stewart, R. H., Lynch, M. G., Crandall, A. S., Mandell, A. I., Wilensky, J. T., Schwartz, A. L., Gaasterland, D. E., deFaller, J. M., and Higginbotham, E. J.: ALO 2145 reduces the intraocular pressure elevation after anterior segment laser surgery. Ophthalmology 95:378, 1988.

20. Robin, A. L., Pollack, I. P., and deFaller, J. M.: Effects of topical ALO 2145 (p-aminoclonidine hydrochloride) on the acute intraocular pressure rise after argon laser iridotomy. Arch. Ophthalmol. 105:1208, 1987.

21. Pollack, I. P., Brown, R. H., Crandall, A. S., Robin, A. L., Stewart, R. H., and White, G. L.: Prevention of the rise in intraocular pressure following neodymium-YAG posterior capsulotomy using topical 1% apraclonidine. Arch. Ophthalmol. 106:754, 1988.

22. Wang, R., Camras, C. B., Podos, S. M., Lee, W., Bhuyan, K. C., and Bhuryan, D. K.: The role of prostaglandins in the para-aminoclonidine–induced reduction of intraocular pressure. Trans. Am. Ophthalmol. Soc. 87:94, 1989.

23. McCannel, C., Koskela, T., and Brubaker, R. F.: Flurbiprofen treatment does not block apraclonidine's effect on aqueous flow. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 148.

Comparison of a 3- and 6-mm Incision in Combined Phacoemulsification and Trabeculectomy

W. Andrew Lyle, M.D., and Jia Chi Jin, M.D.

We studied 216 eyes of 160 patients who underwent combined phacoemulsification and posterior chamber intraocular lens implantation with trabeculectomy. The mean follow-up was 18.7 months, with a minimum follow-up of six months. To assess the safety and efficacy of a recently developed 3-mm incision procedure with foldable intraocular lens implantation (phacotrabeculectomy), we compared 104 eyes subjected to this procedure with 112 eyes subjected to a 6-mm procedure at different follow-up periods. Intraocular pressure control (< 21 mm Hg) was attained in 44 of 46 eyes (96%) in the 3-mm group and 71 of 76 eyes (93%) in the 6-mm group at one year postoperatively. Visual acuity of 20/40 or better was attained in 40 of 46 eyes (87%) in the 3-mm group and 66 of 76 eyes (87%) in the 6-mm group. The incidence of postoperative complication was significantly lower ($P < .001$) and visual acuity in the early postoperative period was significantly better ($P < .01$) in the 3-mm incision group than in the comparison group.

THE ADVANTAGES of combined surgery for cataract and glaucoma have been widely recognized since the mid 1970s.[1-11] Currently, the most commonly used combined procedure is planned extracapsular cataract extraction with a posterior chamber intraocular lens implantation and trabeculectomy.[2-5,9] Phacoemulsification, however, has increased rapidly in popularity recently.[12,13] Since the introduction of foldable lens implantation, some interesting new options are available to anterior segment surgeons. To assess the safety and efficacy of the small incision procedure, we studied the initial experience of a new 3-mm incision procedure for combined phacoemulsification and foldable lens implantation with trabeculectomy and compared 104 eyes subjected to this procedure with 112 eyes subjected to a 6-mm incision conventional combined procedure.

Patients and Methods

The combined phacoemulsification, posterior chamber intraocular lens implantation, and trabeculectomy were performed in 216 eyes of 160 patients by one of us (W.A.L.) between January 1984 and December 1989. Seven eyes of seven additional patients who underwent this operation were excluded from our analysis because of lack of adequate follow-up data collection. In the first group, which began in 1984, all the patients received phacoemulsification with polymethylmethacrylate posterior chamber intraocular lens implantation and trabeculectomy through a 6-mm incision. The trabeculectomy was performed by creating a 3-mm flap posteriorly at one point in the incision. Since March 1988, a new procedure with a 3-mm incision has been used through which the phacoemulsification, intraocular lens insertion, and trabeculectomy are accomplished (phacotrabeculectomy). In our study, 112 eyes in the first group and 104 eyes in the second group were compared.

The criteria for selection of patients were the same in both groups. Those chosen for combined surgery had cataract that affected vision significantly and glaucoma at various stages. The patients had visual field defects consistent with glaucoma, ophthalmoscopic evidence of

Accepted for publication Oct. 19, 1990.
From The Eye Institute of Utah, Salt Lake City, Utah.
Reprint requests to W. Andrew Lyle, M.D., The Eye Institute of Utah, 755 E. 3900 South, Salt Lake City, UT 84107.

glaucomatous optic neuropathy, or intraocular pressure of higher than 22 mm Hg while taking medical treatment. Some of the patients had undergone previous laser trabeculoplasty.

Preoperatively, all patients had a standard examination including best-corrected visual acuity, applanation tonometry, gonioscopy, detailed ophthalmoscopic examination, and visual field testing. Preoperative intraocular pressure was determined as the average of the last three applanation tonometry measurements during the two months before surgery. Postoperative follow-up was at least six months in both groups. Intraocular pressure, best-corrected visual acuity, number of medications, and bleb formation were recorded at each follow-up visit.

3-mm incision procedure—After appropriate local peribulbar anesthesia, a 7-0 silk episcleral traction suture was placed as far superiorly on the globe as possible. A limbal-based conjunctival flap was dissected superiorly approximately 10 mm posterior to the corneoscleral limbus. Tenon's capsule was removed under the area of the conjunctival flap with scissors. The area designated for the scleral trabeculectomy flap was treated with light surface cautery. A 3-mm diamond keratome blade set at a depth of 0.3 mm was used to outline a rectangular trabeculectomy flap measuring 3.0 × 2.5 × 2.5 mm. The posterior edge of this flap was lifted and dissected forward into the corneoscleral limbus with a circular blade. A keratome was used to enter the anterior chamber anteriorly. The irrigating cystotome was introduced, and a circular capsulotomy was performed beginning at the 4 o'clock meridian and carried counterclockwise superiorly to the 12 o'clock meridian. After approximately 180 degrees of capsular tearing had been achieved, the flap was folded over and then pushed inferiorly with the cystotome. The continuous tear capsulotomy was thus carried around to the original starting point at the 4 o'clock meridian. This left the capsular remnant floating free in the anterior chamber. Despite a small pupil, a capsulotomy much larger than the pupil could be fashioned by using viscoelastic material, iris retraction, and visual cues. A 4.5- to 5.0-mm diameter or larger capsulotomy was desired for the silicone lens implant. Phacoemulsification with a 15- or 30-degree tip was used to bisect the nucleus with progressively deeper central sculpting while stabilizing the nucleus with a 5-mm spatula in the other hand. The sculpting was carried deeper centrally until the posterior cortex was reached. Sculpting continued further toward the 6 o'clock meridian until the lower pole of the nucleus was removed. Peripheral portions of the nucleus were then removed by burrowing the phacoemulsification tip into the nucleus and breaking away triangular segments beginning at the 4 o'clock meridian. The segments of nucleus were emulsified in the posterior chamber, and the nucleus was then rotated progressively clockwise with removal of the next triangular segment until the nucleus had been debulked to the point that it could be lifted through the circular capsulotomy and emulsification completed. The cortex was removed by standard irrigation and aspiration handpiece (with occasional use of a curved irrigation and aspiration handpiece of curved cannula for the 12 o'clock cortex). The posterior capsule was vacuumed at a low vacuum setting. Viscoelastic material was injected into the anterior chamber. The silicone intraocular lens was placed into the injector, and the silicone sleeve was slit several times with a blade to allow gentle unfolding of the lens in the eye. At this point, the deep block of corneoscleral tissue was removed by passing the 3-mm diamond blade keratome into the chamber through a second perforation slightly posterior to the original entry. The diamond blade was used to remove a segment of deep sclera. The injector was introduced through the 3-mm incision, and the lens was slowly unfolded into the inferior capsule. Additional viscoelastic material was injected into the anterior chamber to push the upper haptic of the intraocular lens posteriorly. A pusher and microiris hook manipulated the implant into the capsule. The irrigation and aspiration handpiece was used to remove the viscoelastic material with a circular motion in the periphery of the anterior chamber first. This allowed spontaneous rapid washout of most of the central portion of the viscoelastic material. A long, narrow, peripheral iridotomy or iridectomy was performed almost the entire length of the incision. The scleral flap was closed with four to five 10-0 black nylon sutures. The conjunctival incision was sutured with a running 10-0 Prolene (or 8-0 Vicryl) with a blunt vascular–100 needle. Balanced salt solution was injected into the anterior chamber with a 30-gauge cannula through the paracentesis to increase the pressure in the globe. Any conjunctival leaks were closed with additional sutures. Inferior subconjunctival injection of 0.3 mg of betamethasone

was administered. Standard postoperative medications consisted of an antibiotic-corticosteroid eyedrop four to six times daily.

6-mm incision procedure—A 6-mm incision with a central trabeculectomy flap was used. A C-loop or J-loop 6-mm polymethylmethacrylate posterior chamber intraocular lens with 5-0 polypropylene haptics was used in this procedure. Otherwise, the technique was the same as the 3-mm incision procedure.

The preoperative and postoperative care were the same in both groups. Surgery was performed on an outpatient basis and no hospitalization was necessary in either group.

Patients were discharged on the operative day and were examined on the first postoperative day and again at the end of the first postoperative week. Additional follow-up visits were dictated by the clinical course. The patients included in this study were followed up for at least six months after the operation.

The topical antibiotic-corticosteroid eyedrops were gradually discontinued over a six-week period. If adequate filtration or sufficiently low intraocular pressure was not attained after the first four to five days, sutures were cut one at a time with an argon laser and a nylon suture cutting lens. Digital compression by the patient for ten seconds three times daily was recommended if necessary.

Data were analyzed statistically using χ^2 test, Fisher's exact test, and multivariate analysis of variance for repeated measures.

Results

The 3-mm phacotrabeculectomy procedure was performed in 104 eyes of 83 patients, and the 6-mm combined procedure was performed in 112 eyes of 77 patients. The two groups were similar with respect to age (mean, 75.5 years; range, 29 to 97 years), sex (65 men and 95 women), and type of glaucoma (166 of 216 eyes [81.9%] with primary open-angle glaucoma). The duration of postoperative follow-up in the 3-mm group (mean, 11.2 months; range, six to 25 months) was shorter than in the 6-mm group (mean, 26.2 months; range, six to 62 months) (Table 1).

The average preoperative intraocular pressure was 23 mm Hg in both groups, with 55 of the 104 eyes (52.8%) in the 3-mm group having intraocular pressure greater than 22 mm Hg, and 68 of the 112 eyes (60.7%) in the 6-mm group having intraocular pressure greater than 22 mm Hg. Eleven eyes in the 3-mm group and five eyes in the 6-mm group had undergone previous laser trabeculoplasty. The average postoperative intraocular pressure was 16.3 mm Hg at one day, 15.9 mm Hg at one week, 14.3 mm Hg at six months, 15.3 mm Hg at one year, and 14.3 mm Hg at two years in the 3-mm group (Figure).

TABLE 1
PATIENT CHARACTERISTICS

	3-MM INCISION PROCEDURE	6-MM INCISION PROCEDURE	TOTAL
Number of patients	83	77	160
Eyes	104	112	216
Age (yrs)			
Mean	76	75	75.5
Range	38–92	29–97	29–97
Older than 80 years	31	30	61
Sex (M/F)	36/47	29/48	65/95
Follow-up (mos)			
Mean	11.2	26.2	18.7
Range	6–25	6–62	6–62
Subtypes of glaucoma			
Primary open-angle	81	96	177
Pseudoexfoliation	13	11	24
Pigmentary	3	0	3
Combined mechanism	2	2	4
Chronic angle-closure	5	1	6
Trauma-induced	0	2	2

A multivariate analysis of variance for repeated measures was performed on the intraocular pressure measurements. Intraocular pressure of patients included in the analysis was measured at each visit through six months. A significant difference was found between preoperative intraocular pressure and average postoperative intraocular pressure ($P < .001$). There was no significant difference between procedure groups ($P = .744$). However, significant differences were found in the pattern exhibited between procedures over time ($P = .012$). This interaction showed that eyes in the 6-mm procedure group had lower intraocular pressure initially, but eyes in the 3-mm procedure group ultimately had lower intraocular pressure (Table 2). At the first postoperative day, ten of 104 eyes (9.6%) in the 3-mm group and seven of 112 eyes (6.3%) in the 6-mm group

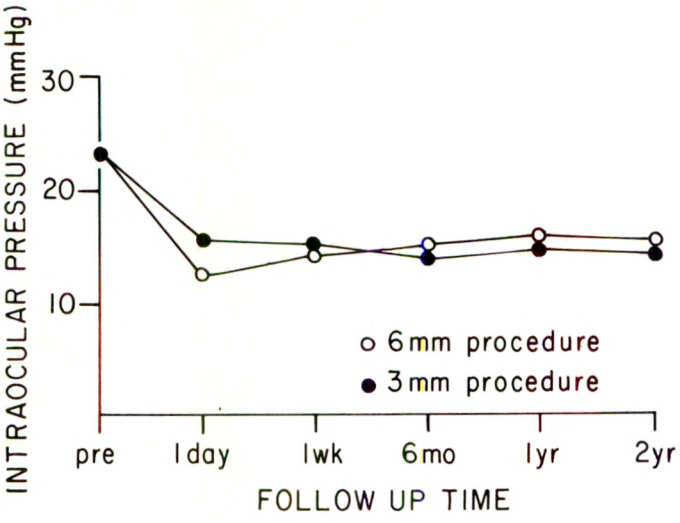


Figure (Lyle and Jin). Intraocular pressure at different follow-up periods for 3-mm and 6-mm groups. Note that the 3-mm procedure had lower intraocular pressure ultimately.

had intraocular pressure greater than 30 mm Hg. At the one-year follow-up visit, 44 of 46 eyes (96%) in the 3-mm group and 71 of 76 eyes (93%) in the 6-mm group had intraocular pressure of less than or equal to 21 mm Hg (Table 3).

The number of antiglaucoma medications before and after surgery is shown in Table 4. A substantial decrease in the number of medications after surgery occurred. Preoperatively, 96 of 104 eyes (92.3%) in the 3-mm group required medication. At six months and one year postoperatively, 82 of 104 eyes (78.8%) and 36 of 46 eyes (78.3%) did not require medications to control intraocular pressure, respectively. In the 6-mm group, 109 of 112 eyes (96.4%) required preoperative medication. At six months and one year postoperatively, 68 of 110 eyes (61.8%) and 44 of 76 eyes (57.9%) did not require medications to control intraocular pressure, respectively. There was a significant difference regarding the medication between these two groups at the one-year postoperative period ($P < .05$) (Table 4).

TABLE 2
INTRAOCULAR PRESSURE CHANGE AFTER SURGERY*

PROCEDURE	PREOPERATIVE INTRAOCULAR PRESSURE (MM HG)	CHANGE IN INTRAOCULAR PRESSURE (MM HG) DAY 1	WEEK 1	MONTH 6	AVERAGE CHANGE FOR PROCEDURE
3-mm incision (N=94)	23.10	−7.78	−7.61	−8.95	−8.11
6-mm incision (N=97)	23.00	−9.86	−6.74	−6.79	−7.79
Average change at time period (N=191)		−8.82	−7.17	−7.87	−7.95

*The P values were as follows: procedure, P = .744; constant, P = .0001; effect, P = .137; and P × E, P = .012.

At the first postoperative day, 29 of 104 eyes (27.9%) in the 3-mm group had visual acuity of 20/40 or better, compared to 14 of 112 eyes (12.5%) in the 6-mm group. There was a significant difference between these two groups ($P < .01$). At the six-month visit, 89 of 104 eyes (85.6%) in the 3-mm group had 20/40 visual acuity or better as compared to 87 of 112 eyes (77.7%) in the 6-mm group. At the 12-month postoperative interval, 40 of 46 eyes (87%) in the 3-mm group and 66 of 76 eyes (87%) in the 6-mm group had visual acuity of 20/40 or better (Table 5).

There were six eyes in the 3-mm group and eight eyes in the 6-mm group that retained the same visual acuity as preoperatively or deteriorated at the final follow-up visit. The mean follow-up time was nine months in the 3-mm group and 45 months in the 6-mm group. Among those 14 eyes with visual acuity worse than 20/200, four were believed to have central vision involvement by advanced glaucoma preoperatively, eight had age-related macular degeneration, one had central retinal vein occlusion, and one had cystoid macular edema.

TABLE 3
INTRAOCULAR PRESSURE CONTROL AT EACH FOLLOW-UP VISIT

	3-MM PROCEDURE				6-MM PROCEDURE			
INTRAOCULAR PRESSURE	PREOPERATIVE (N = 104) NO. (%)	6 MONTH (N = 104) NO. (%)	12 MONTH (N = 46) NO. (%)	24 MONTH (N = 14) NO. (%)	PREOPERATIVE (N = 112) NO. (%)	6 MONTH (N = 110) NO. (%)	12 MONTH (N = 76) NO. (%)	24 MONTH (N = 63) NO. (%)
≤ 21 mm Hg	49 (47.1)	102 (98)	44 (95.6)	14 (100)	44 (39.3)	105 (95.4)	71 (93.4)	58 (92.1)
> 22 mm Hg	55 (52.9)	2 (1.9)	2 (4.3)	0 (0.0)	68 (60.7)	5 (4.5)	5 (6.6)	5 (7.9)

A detectable conjunctival filtering bleb was seen in 22 of 104 eyes (21.1%) in the 3-mm group and 27 of 110 eyes (24.5%) in the 6-mm group at the six-month visit, and in nine of 46 eyes (19.5%) in the 3-mm group and ten of 76 eyes (13.2%) in the 6-mm group at the 12-month visit. No statistical difference was noted between the two groups ($P > .98$ at six months and $P > .30$ at 12 months).

The most frequent complication was transient postoperative hyphema, which occurred in 15 of 104 eyes (14.4%) in the 3-mm group and 30 of 112 eyes (26.8%) in the 6-mm group. All spontaneously cleared within seven days without detrimental effect. A statistically significant difference was noted between the two groups ($P = .039$). Posterior capsular opacification that required Nd:YAG posterior capsulotomy occurred in ten eyes (9.6%) in the 3-mm group and 20 eyes (17.9%) in the 6-mm group ($P = .120$). Postoperative choroidal effusion occurred in three of 104 eyes (2.3%) in the 3-mm group, which was significantly lower as compared with 13 of 113 eyes (11.6%) in the 6-mm group ($P = .029$). The choroidal effusion was readily absorbed within three weeks in all patients after corticosteroid and cycloplegic treatment without surgical intervention. Posterior synechiae developed in four eyes in the 6-mm group and in none of the eyes in the 3-mm group, and cystoid macular edema occurred in one eye in the 3-mm group and four eyes in the 6-mm group (Table 6).

Discussion

The surgical treatment of cataract in patients with glaucoma has changed because of the widespread use of extracapsular extraction, posterior chamber intraocular lens implantation, and trabeculectomy.[1-11] Recently, these techniques have been modified with the resurgence of phacoemulsification,[12,13] which we have used in combined cataract and glaucoma procedures since 1984. We have performed a new 3-mm incision procedure using phacoemulsification, foldable lens implantation, and trabeculectomy in our patients since 1988.

The postoperative results of 104 eyes in the 3-mm incision group and 112 eyes in the 6-mm procedure group were encouraging in comparison to previous studies with planned extracapsular extraction and trabeculectomy. The long-term intraocular pressure control was similar in our two groups, with mean preoperative intraocular pressure of 23 mm Hg in both groups;

TABLE 4
ANTIGLAUCOMA MEDICATION

	3-MM PROCEDURE				6-MM PROCEDURE			
NO. OF MEDICATIONS	PREOPERATIVE (N = 104) NO. (%)	6 MONTH (N = 104) NO. (%)	12 MONTH (N = 46) NO. (%)	24 MONTH (N = 14) NO. (%)	PREOPERATIVE (N = 112) NO. (%)	6 MONTH (N = 110) NO. (%)	12 MONTH (N = 76) NO. (%)	24 MONTH (N = 63) NO. (%)
0	8 (7.7)	82 (78.8)	36 (78.3)	8 (57.1)	4 (3.6)	68 (61.8)	44 (57.9)	30 (47.6)
1	67 (64.4)	20 (19.2)	8 (17.4)	4 (28.6)	62 (55.4)	36 (32.7)	26 (34.2)	29 (46.0)
2	25 (24.0)	2 (1.9)	2 (4.3)	2 (14.3)	36 (32.1)	6 (5.5)	6 (7.9)	4 (6.3)
3 or more	4 (3.8)	0	0	0	10 (8.9)	0	0	0

TABLE 5
PREOPERATIVE AND POSTOPERATIVE VISUAL ACUITY

	3-MM PROCEDURE						6-MM PROCEDURE					
VISUAL ACUITY*	PREOPERATIVE (N = 104) NO. (%)	1 DAY (N = 104) NO. (%)	1 WEEK (N = 100) NO. (%)	6 MONTHS (N = 104) NO. (%)	1 YEAR (N = 46) NO. (%)	2 YEARS (N = 14) NO. (%)	PREOPERATIVE (N = 112) NO. (%)	1 DAY (N = 112) NO. (%)	1 WEEK (N = 103) NO. (%)	6 MONTHS (N = 110) NO. (%)	1 YEAR (N = 76) NO. (%)	2 YEARS (N = 63) NO. (%)
20/25	0	9 (8.7)	17 (17.0)	54 (51.9)	23 (50.0)	9 (57.1)	1 (0.9)	1 (0.89)	9 (8.7)	47 (42.7)	38 (50.0)	28 (44.4)
20/30–20/40	21 (20.2)	20 (19.2)	35 (35.0)	35 (33.7)	17 (37.0)	5 (35.7)	11 (9.8)	13 (11.6)	29 (28.2)	40 (36.4)	28 (36.8)	28 (36.5)
20/50–20/70	53 (51.0)	25 (24.0)	23 (23.0)	10 (9.6)	2 (4.3)	0	63 (56.3)	24 (21.4)	29 (28.2)	17 (15.5)	5 (6.6)	6 (9.5)
20/80–20/100	13 (2.5)	10 (9.6)	10 (10.0)	0	1 (2.2)	1 (7.1)	17 (15.2)	17 (15.2)	10 (9.7)	3 (2.7)	1 (1.3)	2 (3.2)
20/200–CF	14 (13.5)	36 (34.6)	13 (13.0)	5 (4.8)	3 (6.5)	0	16 (14.3)	34 (30.4)	17 (16.5)	3 (3.7)	3 (3.9)	3 (4.8)
HM or worse	3 (2.9)	4 (3.8)	2 (2.0)	1 (0.9)	0	0	4 (3.6)	23 (20.5)	9 (8.7)	4 (3.6)	1 (1.3)	1 (1.6)

*CF indicates counting fingers and HM indicates hand motions.

14.3 mm Hg at six months, 15.8 mm Hg at one year, and 14.3 mm Hg at two years in the 3-mm group; and 15.8 mm Hg at six months, 17.5 mm Hg at one year, and 16.1 mm Hg at two years in the 6-mm group. These results were consistent with that of Murchison and Shields[2] (mean baseline intraocular pressure, 18 mm Hg; mean final intraocular pressure, 14.7 mm Hg), and McCartney and associates[3] (mean baseline intraocular pressure, 23 mm Hg; mean final intraocular pressure, 17.1 mm Hg). In the present study, at one year, 36 of 46 eyes (78.3%) attained intraocular pressure control (≤ 21 mm Hg) on no medication, 17.4% were controlled on one medication, and 4.3% had intraocular pressure of 22 mm Hg in the 3-mm group. In comparison to the 6-mm group and the study of McCartney and associates[3] (both had 57% of eyes ≤ 21 mm Hg without medication), there were fewer medications needed to control intraocular pressure in the 3-mm group. The 6-mm procedure had lower intraocular pressure initially, but the 3-mm procedure ultimately showed lower intraocular pressure.

There was obvious improvement of visual acuity in both groups compared to the preoperative vision. At one year after surgery, 87% of eyes in both groups (40 of 46 eyes in the 3-mm

TABLE 6
COMPLICATION

	3-MM INCISION (N = 104)		6-MM PROCEDURE (N = 112)		
COMPLICATIONS	NO.	(%)	NO.	(%)	DIFFERENCE
Hyphema	15	(14.4)	30	(26.8)	P = .03866
Shallow anterior chamber	3	(2.9)	17	(15.2)	P = .00398
Posterior chamber opacification requiring YAG posterior capsulotomy	10	(9.6)	20	(17.9)	P = .12038
Choroidal detachment	3	(2.9)	13	(11.6)	P = .02883
Intraocular pressure increase (≥ 30 mm Hg)	10	(9.6)	7	(6.3)	P = .51573
Hypotony (≤ 4 mm Hg)	3	(2.9)	15	(13.4)	P = .01091
Cystoid macular edema	1	(0.9)	4	(3.6)	P = .3709
Posterior synechiae	0	(0)	4	(3.6)	P = .123
No complication	56	(53.8)	30	(26.8)	P = .0001

group and 66 of 76 eyes in the 6-mm group) attained visual acuity of 20/40 or better. This finding is favorable compared to Simmons and associates,[4] who noted that 33 of 55 eyes (60%) of their patients had visual acuity of 20/40 or better at one year, and Murchison and Shields,[2] who found that 17 of 22 eyes (77%) of their patients attained visual acuity of 20/50 or better with a limbal-based conjunctival flap. At the first postoperative day, 27.9% (29 eyes) in the 3-mm group and 12.5% (14 eyes) in the 6-mm group had visual acuity of 20/40 or better. There was a significant difference between these two groups ($P < .01$). The 3-mm incision procedure provided better visual acuity than the 6-mm incision in the early postoperative stage. Among the 14 patients with worse visual acuity, 57% (eight eyes) had age-related macular degeneration and 28.5% (four eyes) had advanced glaucoma damage that existed preoperatively.

The 3-mm incision has theoretical advantages over large incision surgery including decreased astigmatism, better uncorrected visual acuity, more rapid stabilization of refraction, shorter operating time, and more rapid healing. In our series, visual acuity on the first postoperative day was significantly better in the 3-mm group (with visual acuity of 20/40 or better in 27.9% and 12.5% of eyes in each group, respectively; $P < .01$), and the incidence of early complications was much less ($P < .001$). Patient discomfort was rare, all of our patients were treated on an outpatient basis, and no patient had severe complications caused by early discharge and early activities.

Postoperative hyphema is the most common complication in combined surgery. The fixed and immobile pupil from prolonged miotic therapy may result in bleeding caused by iris stretching and trauma during cataract extraction.[4] Bleeding can also occur from the corneoscleral incision or the iris. The incidence of hyphema has varied in published reports. Simmons and associates[4] reported a hyphema rate of 45%, with 71% of hyphemas occurring in limbal-based flaps and 30% occurring in fornix-based flaps. Murchison and Shields[2] reported that hyphema occurred in 28% of their patients after combined surgery, which is similar to the findings in our 6-mm group in which 30 eyes (26.8%) had hyphema. In the small incision group, however, only 15 eyes (14.4%) had hyphema during the early postoperative course. There was a significant difference between these two groups ($P = .039$). One patient in the 3-mm incision group developed a hyphema after suture cutting with the argon laser.

The rate of posterior capsular opacification requiring capsulotomy was 17.9% (20 of 112 eyes) in the 6-mm incision group, which agreed with previous studies,[2-4] but it was reduced in the small incision group with a rate of 9.6% (ten of 104 eyes).

Choroidal detachments occur frequently after glaucoma procedures during the early postoperative period[8-11,14-16] when hypotony permits transudation of fluid across the capillary walls of the choroid and collects on the potential space between uvea and sclera.[16] This may result in a shallow or flat anterior chamber. Choroidal detachment occurred in six eyes (6%) with combined surgery in the report of McCartney and associates.[3] In our series, three eyes (2.9%) and 13 eyes (11.6%) had choroidal detachment in the 3-mm incision group and the 6-mm incision procedure group, respectively.

The prevalence of shallow or flat anterior chamber occurring after combined surgery has been previously reported as being between 5% and 26%.[3-6] We found a significant difference between the 3-mm incision group and 6-mm incision group (2.9% and 15.2%, respectively; $P = .004$).

The combined procedure may benefit patients with glaucoma and cataract by protection against severe early intraocular pressure increase.[6] Simmons and associates[4] reported that 36% of patients had early postoperative intraocular pressure greater than 30 mm Hg and 40% had intraocular pressure 7 mm Hg above their preoperative level despite combined surgery, compared to the reported incidence of up to 72% in patients with glaucoma undergoing cataract surgery alone.[8] McCartney and associates[3] showed that 5% of their combined surgery patients had intraocular pressure increase of 35 mm Hg, and Murchison and Shields[2] noted 8.5% of eyes had intraocular pressure increase greater than 30 mm Hg in the early postoperative period. In our study, there were ten of 104 eyes (9.6%) and seven of 112 eyes (6.3%) that had intraocular pressure increase ($\geq$ 30 mm Hg) in the 3-mm incision group and 6-mm procedure group at the first postoperative day, respectively. The highest intraocular pressure, 66 mm Hg, occurred in an eye that received intensive treatment with 20% mannitol intravenous injection and acetazolamide intravenous injection, and intraocular pressure decreased to 17 mm Hg the next day and was controlled well afterward.

In our series, the presence of a detectable conjunctival filtering bleb postoperatively was favorable compared with previous studies. In the study of Murchison and Shields,[2] only 23% to 24% of eyes had filtering blebs at two months postoperatively. Simmons and associates[4] reported 12% of eyes had detectable blebs at 12 months. In our series, 22 eyes (21.1%) in the 3-mm incision group and 27 eyes (24.5%) in the 6-mm incision group had detectable filtering blebs at six months, and nine eyes (19.6%) in the 3-mm group and ten eyes (13.2%) in the 6-mm group had blebs at 12 months.

One of the common problems with combined cataract and glaucoma surgery is the miotic pupil. In our series, we performed the technique of circular capsulotomy with a capsular phacoemulsification without further modification. It is possible to use phacoemulsification on a pupil measuring 2.75 mm, but this can be tedious. Alternatives include multiple sphincterotomies at the pupil, radial iridotomy with or without resuture of the iris, and small sector iridectomy. Multiple sphincterotomies can be done with or without viscoelastic material by making small incisions in the pupil in enough locations to dilate the pupil adequately. A radial iridotomy is carried out after first performing a peripheral iridectomy. The iris pillars are swept aside for phacoemulsification and can then be resutured with 10-0 polypropylene if desired. A small sector iridectomy is done by introducing viscoelastic material into the anterior chamber, followed by several applications of a Descemet membrane punch at the superior margin of the iris. This allows enlargement of the pupil and gives good cosmetic results postoperatively.

References

1. Rich, W.: Cataract extraction with trabeculectomy. Trans. Ophthalmol. Soc. U.K. 94:458, 1974.

2. Murchison, J. F., Jr., and Shields, M. B.: Limbal-based vs fornix-based conjunctival flaps in combined extracapsular cataract surgery and glaucoma filtering procedure. Am. J. Ophthalmol. 109:709, 1990.

3. McCartney, D. L., Memmen, J. E., Stark, W. J., Quigley, H. A., Maumenee, A. E., Gottsch, J. D., Bernitsky, D. A., and Wong, S. K.: The efficacy and safety of combined trabeculectomy, cataract extraction, and intraocular lens implantation. Ophthalmology 95:754, 1988.

4. Simmons, S. T., Litoff, D., Nichols, D. A., Sherwood, M. B., and Spaeth, G. L.: Extracapsular cataract extraction and posterior chamber intraocular lens implantation combined with trabeculectomy in patients with glaucoma. Am. J. Ophthalmol. 104:465, 1987.

5. Shields, M. B.: Combined cataract extraction and guarded sclerectomy. Re-evaluation in the extracapsular era. Ophthalmology 93:366, 1986.

6. Spaeth, G. L., and Sivalingam, E.: The partial-punch. A new combined cataract-glaucoma operation. Ophthalmic Surg. 7:53, 1976.

7. Edwards, R. S.: Trabeculectomy combined with cataract extraction. A follow-up study. Br. J. Ophthalmol. 64:720, 1980.

8. Savage, J. A., Thomas, J. V., Belcher, C. D., III, and Simmons, R. J.: Extracapsular cataract extraction and posterior chamber intraocular lens implantation in glaucomatous eyes. Ophthalmology 92:1506, 1985.

9. Willamson, T. H., Bacon, A. S., Flanagan, D. W., Jakeman, C. M., and Jordon, K.: Combined extracapsular cataract extraction and trabeculectomy using a separated corneal section. Eye 3:547, 1989.

10. Jay, J. L.: Extracapsular lens extraction and posterior chamber lens insertion combined with trabeculectomy. Br. J. Ophthalmol. 69:487, 1985.

11. McGuigan, L. J. B., Gottsch, J., Stark, W. J., Maumenee, A. E., and Quigley, H. A.: Extracapsular cataract extraction with posterior chamber lens implantation in eyes with pre-existing glaucoma. Arch. Ophthalmol. 104:1301, 1986.

12. Cohen, J. S.: Combined cataract implant and filtering surgery with 5-fluorouracil. Ophthalmic Surg. 21:181, 1990.

13. Tsutomu, H., and Takako, H.: Endocapsular phacoemulsification and aspiration (ECPEA). Recent surgical technique and clinical results. Ophthalmic Surg. 20:469, 1989.

14. Neumann, R., Zalish, R. N., and Oliver, M.: Effect of intraocular lens implantation on combined extracapsular cataract extraction with trabeculectomy. A comparative study. Br. J. Ophthalmol. 72:741, 1988.

15. Percival, S. P. B.: Glaucoma triple procedure of extracapsular cataract extraction, posterior chamber lens implantation, and trabeculectomy. Br. J. Ophthalmol. 69:99, 1985.

16. Berke, S. J., Bellows, A. B., Shingleton, B. J., Richter, C. U., and Hutchinson, B. T.: Chronic and recurrent choroidal detachment after glaucoma filtering surgery. Ophthalmology 94:154, 1987.

Tissue Plasminogen Activator Treatment of Experimental Subretinal Hemorrhage

Hilel Lewis, M.D., Steven C. Resnick, M.D., John G. Flannery, Ph.D., and Bradley R. Straatsma, M.D.

To determine if tissue plasminogen activator, a clot-specific fibrinolytic agent, could eventually be used to assist in the clearance or removal of subretinal hemorrhage, we studied the effect of subretinal injections of tissue plasminogen activator, autologous blood, balanced salt solution, and the combination of either tissue plasminogen activator or balanced salt solution after subretinal injection of autologous blood on retinal morphologic characteristics and clearance of subretinal hemorrhage in the albino rabbit. No morphologic evidence of tissue plasminogen activator toxicity was found in the rabbit retina at a dose of 25 to 50 μg/0.1 ml. Subretinal hemorrhage cleared faster after subretinal injection of tissue plasminogen activator when compared to balanced salt solution (P = .0005) but did not completely prevent overlying retinal degeneration. Both tissue plasminogen activator and balanced salt solution were found to decrease the toxic effects of subretinal blood on the morphologic characteristics of the rabbit retina, and this effect can be explained at least partly by dilution of the subretinal blood.

SUBRETINAL HEMORRHAGE associated with retinochoroidal disease or occurring during retinal or vitreous surgery is a potentially serious problem that may lead to severe visual loss.[1] Currently, most patients with subretinal hemorrhage do not receive any treatment. Surgical evacuation of the hemorrhage or clot has been performed but, in most cases, has not produced satisfactory visual results.[2] The retinal damage from the subretinal hemorrhage may result from the diffusion barrier formed by the clot, toxicity to iron released from red blood cells, and from mechanical damage to the photoreceptor cells caused by contraction of the clot.[3,4] Therefore, it is possible that this retinal damage could be prevented or decreased by pharmacologically dissolving the fibrin matrix within the clot. Purified human tissue plasminogen activator produced by recombinant DNA technology is currently available for use in patients and is theoretically of benefit in the lysis of fibrin clots.[5-11] We studied the safety and effectiveness of tissue plasminogen activator in the experimental clearance of subretinal hemorrhage.

Material and Methods

New Zealand white rabbits were used. The animals were handled according to the Association for Research in Vision and Ophthalmology resolution on the use of animals, and the study was approved by the UCLA Animal Review Committee. The rabbits were anesthetized with intramuscular xylazine hydrochloride (5 mg/kg of body weight) and ketamine hydrochloride (35 mg/kg of body weight). Mydriasis was produced with 5% phenylephrine and 0.25% tropicamide. Topical proparacaine hydrochloride was placed on the globes, then the recti muscles were isolated, and sutures were placed so as to be able to obtain optimal ocular mobility. A modification of the technique used by Glatt and Machemer[3] to inject subretinal blood was used. A 30-gauge needle attached to a tuberculin syringe was inserted through the sclera and choroid, and tissue plasminogen activator, balanced salt solution, blood, or a combination of these, were injected into the subretinal space under the medullary ray and under direct visual guidance of the operating microscope.

Accepted for publication Oct. 18, 1990.

From the Jules Stein Eye Institute, and Department of Ophthalmology, UCLA School of Medicine, Los Angeles, California. This study was supported by the John and Theiline McCone Macular Disease Research Fund and the Charles Kenneth Feldman Fund.

Reprint requests to Hilel Lewis, M.D., Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90024-7007.

There were two experimental groups. In Group 1, we injected, in a masked fashion, 12 eyes with 25 μg/0.1 ml of tissue plasminogen activator, 12 eyes with 50 μg/0.1 ml of tissue plasminogen activator, and 12 eyes with 0.1 ml of sterile balanced salt solution. In Group 2, 24 eyes received a subretinal injection of autologous blood (0.1 ml) alone, and 48 eyes received a subretinal injection of autologous blood (0.1 ml), and 30 minutes later, after a subretinal clot had formed, we injected either 25 μg/0.1 ml of tissue plasminogen activator (24 eyes) or 0.1 ml of balanced salt solution (24 eyes) in the same subretinal space as the previously formed blood clot. The subretinal injection created a dome-shaped elevation measuring 3 to 5 disk diameters in area and 2 to 3 disk diameters in height.

The recombinant tissue plasminogen activator had an average activity of 580 IU/μg and a pH of 7.3. The vehicle consisted of 35 mg/ml of L-arginine phosphate, 10 mg/ml of phosphoric acid, and polysorbate 80. To prepare the drug for injection, tissue plasminogen activator was reconstituted according to the manufacturer's recommendations to give a concentration of 50 mg/50 ml. This solution was then diluted four-fold, divided into multiple aliquots, and frozen at −70 C until immediately before use, when it was warmed at room temperature and diluted in sterile balanced salt solution to concentrations of 25 and 50 μg/0.1 ml. The balanced salt solution was sterile and did not contain calcium or magnesium. The autologous blood was obtained from the rabbit's ear with a 30-gauge butterfly needle attached to a tuberculin syringe. After collection, the blood was injected immediately into the subretinal space. The blood was collected and injected rapidly to avoid using an anticoagulant in the syringe.

After injection, the eyes were examined daily with indirect ophthalmoscopy until they were enucleated immediately after killing the rabbit with 5 ml of pentobarbital sodium. In Group 1, four eyes of each of the three subgroups were enucleated at Day 1, four eyes were enucleated at Day 3, and the remaining four eyes were enucleated at Day 7 after subretinal injection. In Group 2, 12 eyes of each of the three subgroups were followed up until the subretinal blood had completely cleared, and the eyes were then enucleated. Of the remaining 12 eyes of each subgroup, four eyes were enucleated at Day 1, four eyes at Day 3, and four eyes at Day 7.

After enucleation, the anterior segment was removed, and the posterior eyecup was placed in a solution of 2.5% glutaraldehyde and 2% formaldehyde in 0.1 mol/l of sodium phosphate buffer at pH 7.2. The aldehyde-fixed posterior eyecup was postfixed in 1% osmium tetroxide, dehydrated in a graded series of methanol, and embedded in Araldite resin for light and electron microscopy.

For light microscopy, 1-μm sections from regions embedded in Araldite were stained with toluidine blue. The retinas were sectioned serially through the area where the subretinal tissue plasminogen activator, balanced salt solution, or blood was injected. Photomicrographs were taken at a magnification of × 25 and × 40 with a photomicroscope. Electron microscopy was performed on thin sections (40 nm) stained with uranyl acetate and lead citrate and examined with an electron microscope. Indirect ophthalmoscopy and histopathologic studies were performed by a masked examiner.

Time (in days) to clearance of subretinal blood was an outcome analyzed. Statistical comparisons were performed with nonparametric tests (Mann-Whitney rank-sum test, Wilcoxon signed-rank test), because the time values had a skewed distribution.

Results

Immediately after the injection of either tissue plasminogen activator, balanced salt solution, or autologous blood, a subretinal bleb measuring between 3 and 5 disk diameters in area and 2 to 3 disk diameters in height was produced.

The subretinal bleb flattened at a median of 14 hours in eyes receiving 25 μg/0.1 ml of tissue plasminogen activator, 15 hours in eyes receiving 50 μg/0.1 ml of tissue plasminogen activator, and 11 hours in eyes receiving 0.1 ml of balanced salt solution. After enucleation, gross examination of the fundus disclosed a normal appearance with regular pigmentation at the level of the retinal pigment epithelium over the whole fundus. The optic nerve and retinal blood vessels appeared to be normal, and there was no evidence of pigment migration into the neurosensory retina. There were no differences in gross morphologic characteristics between eyes that received different dosages of tissue plasminogen activator or between these eyes and the controls (balanced salt solution). The appearance of the fundus was similar one, three, and seven days after subretinal

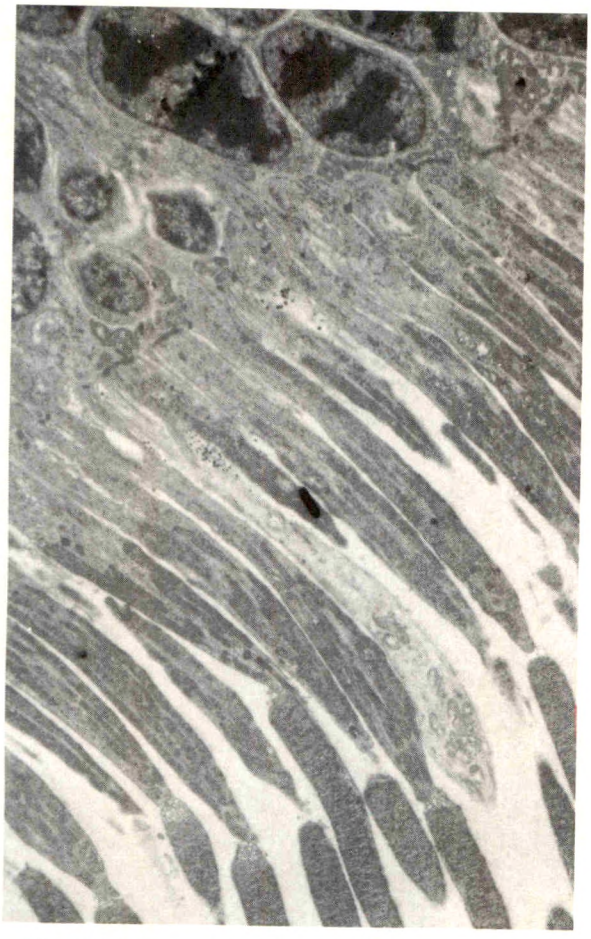


Fig. 1 (Lewis and associates). Electron micrograph one day after subretinal injection of 50 μg/0.1 ml of tissue plasminogen activator demonstrates well-preserved photoreceptors with well-ordered outer segments overlying the region of retinal detachment (× 1,200).

injection. On light and electron microscopy, the retinal pigment epithelium was seen as a monolayer in all areas of the eye examined and was regular in thickness and pigmentation in all areas. In the region of the retinal detachment caused by subretinal injection of either tissue plasminogen activator or balanced salt solution, there was some loss of the surface specialization of the apical membrane of the retinal pigment epithelium, which has been described as a normal consequence of short-term retinal detachment.[12] The shape of the basal retinal pigment epithelium membrane apposed to Bruch's membrane appeared unaltered. Proliferative changes in the retinal pigment epithelium monolayer were not observed. The photoreceptors appeared normal in number and length (Fig. 1). Ultrastructural examination disclosed some mechanical disruption of the orderly stacking of the outer segment disks in the area of the subretinal injection, but there were no signs of changes in the overall packing density of receptors from that in the control. The nuclei of the photoreceptors were normal in appearance. Few inclusion bodies or autophagic vacuoles were noticed within the photoreceptors. Ultrastructural abnormalities that are commonly associated with drug toxicity, such as the presence of vesicles in place of the most basal disks and swollen inner segment mitochondria, were not seen. The subretinal space in the region of the injection contained some outer segment debris and a few erythrocytes but no other cell types. Bruch's membrane and the choriocapillaris were normal over all of the fundus. The transition to normal retinal pigment epithelium and photoreceptors with well-ordered outer segments at the edge of the subretinal bleb was abrupt.

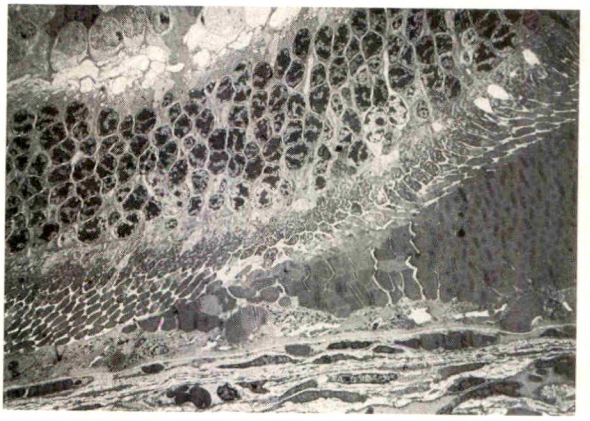


Fig. 2 (Lewis and associates). Electron micrograph one day after subretinal injection of 0.1 ml of autologous blood shows at the edge of the subretinal clot a sharp transition between retina with relatively intact photoreceptors and a region characterized by disorganization of the photoreceptor layer (× 880).

Eyes that were injected with autologous blood only had a subretinal bleb in which the clot separated into different layers with a central dark zone and a surrounding area of light red color. The subretinal blebs of the eyes that received autologous blood followed by either tissue plasminogen activator or balanced salt solution were larger, and in contrast to eyes with autologous blood only, were more homogeneous with no layering seen a few hours after injection.

The time to complete ophthalmoscopic clearance of subretinal blood was 20 to 32 days (median, 28.5 days) in eyes that received autol-

ogous blood only; 11 to 16 days (median, 14 days) in eyes that received autologous blood and tissue plasminogen activator; and 15 to 23 days (median, 19 days) in eyes that received autologous blood and balanced salt solution. The faster clearance of subretinal hemorrhage in eyes treated with either tissue plasminogen activator ($P = .0007$) or balanced salt solution ($P = .0007$) was statistically significant when compared to eyes injected with autologous blood alone (Mann-Whitney rank-sum test). There was also a statistically significant faster clearance of subretinal hemorrhage in eyes treated with tissue plasminogen activator ($P = .0005$) when compared to those treated with balanced salt solution (Wilcoxon signed-rank test).

Examination of the fundus by light and electron microscopy one day after the injection of autologous blood alone showed the disruption of the photoreceptor layer to be greatest in regions containing uninterrupted blood and a high detachment of the neurosensory retina from the retinal pigment epithelium. At the edges of the clot, where the distance of separation was not as great, numerous photoreceptors were intact and organized but shortened outer segments were present (Fig. 2). In the transition from attached retina to the central region of the clot, all photoreceptor outer segments were lost, and the inner segments became increasingly abnormal in appearance. As the separation of the neural retina from the retinal pigment epithelium increased, the proportion of severely altered photoreceptors also increased, with morphologic changes to both the inner and outer segments. The central region of the clot (Fig. 3) was characterized by disordered photoreceptors and many pyknotic nuclei in the inner layers of the neurosensory retina. Much of the central region of the subretinal blood was completely devoid of photoreceptor cells. In these cases, the outer nuclear layer abutted the clot directly. There was little gliosis in degenerated retina, but there were regions of severe vacuolization and cystoid space formation. The inner nuclear layer was intact. The retinal pigment epithelium was seen as a monolayer in all of the eyes and was regular in thickness and pigmentation in all areas. Bruch's membrane and the choriocapillaris were normal in all areas. At Day 3, Day 7, and after clearance of subretinal blood, the histopathologic examination demonstrated progressive degeneration of the retina with loss of photoreceptors in the area of subretinal injection.

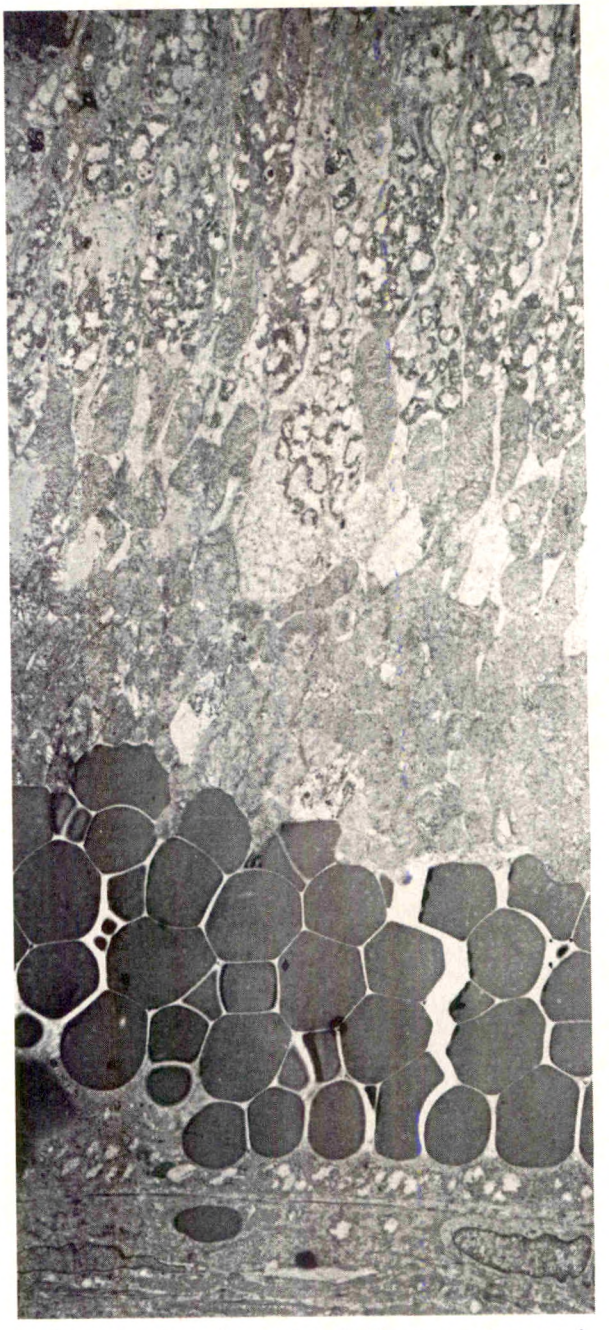


Fig. 3 (Lewis and associates). Electron micrograph of the central region of the subretinal clot three days after injection of 0.1 ml of autologous blood with profound atrophy of the photoreceptor layer, characterized by disorganization of the outer segments and disruption of the inner segments. The retinal pigment epithelium is irregular in thickness and highly vacuolized throughout (× 1,800).

Eyes that received tissue plasminogen activator or balanced salt solution subsequent to the injection of autologous blood showed less dam-

age to the retina at each interval when compared to eyes injected with autologous blood alone. In these eyes, the morphologic characteristics of the subretinal clot was altered markedly, with many identifiable single blood cells in a diffuse array. This contrasted with the appearance of a solid continuous clot, devoid of individual cells, which was seen in all eyes injected with subretinal blood alone. Photoreceptors overlying regions treated with tissue plasminogen activator or balanced salt solution after injection of subretinal blood were less severely disorganized than cells in corresponding regions of the eye receiving autologous blood alone. In much of the affected retina, the subretinal space appeared clear, and numerous truncated outer segments were present. After clearing of the subretinal blood, the edges of the detached retina were characterized by the reappearance of photoreceptor outer segments and reestablishment of the normal level between the neural retina and the apical membrane of the retinal pigment epithelium. The eyes receiving subretinal blood and tissue plasminogen activator or balanced salt solution generally sustained less degenerative change in retinal appearance than those with blood alone and retained substantial numbers of photoreceptors that had well-organized outer segments (Fig. 4). In these eyes, the retinal pigment epithelium also was observed to retain a normal appearance (Fig. 5). There were no significant morphologic differences between eyes with subretinal hemorrhage treated with tissue plasminogen activator and those treated with balanced salt solution.



Fig. 4 (Lewis and associates). Electron micrograph of an eye seven days after injection of subretinal autologous blood (0.1 ml) followed by tissue plasminogen activator (25 μg/0.1 ml). Photoreceptors with well-ordered outer segments are seen overlying the area of retinal separation.

Discussion

Subretinal hemorrhages can occur from many causes, including choroidal neovascularization from degenerative, infectious, dystrophic, inflammatory, traumatic, iatrogenic, and idiopathic conditions; and complications from surgical procedures, such as scleral buckling, endodrainage retinotomies, and photocoagulation. Evidence suggests that subretinal blood causes irreversible damage to the retina and is associated with poor visual function if it involves the fovea.[3] Prognostic features for visual outcome include the cause of the subretinal hemorrhage, as well as its location and thickness.[1] Bennet, Blodi, and Folk[1] showed that patients with subretinal hemorrhage caused by age-related macular degeneration have a worse visual prognosis than those with hemorrhage from other causes. They also found that patients with thick hemorrhage have a significantly poorer final visual acuity than patients with thin hemorrhage. Although some patients with subretinal hemorrhage have a good visual prognosis (that is, those with a thin layer of subretinal blood or those caused by choroidal rupture), the visual prognosis for most eyes with a subretinal hemorrhage is poor with an average final visual acuity of 20/500 after three years.[1]

Recent advances in vitreoretinal surgical techniques have made it possible to evacuate subretinal hemorrhage, and cases have been reported in which surgery to drain a subretinal hemorrhage under the macula was performed in an attempt to improve visual acuity.[2,13,14] Moreover, it has been suggested that prompt

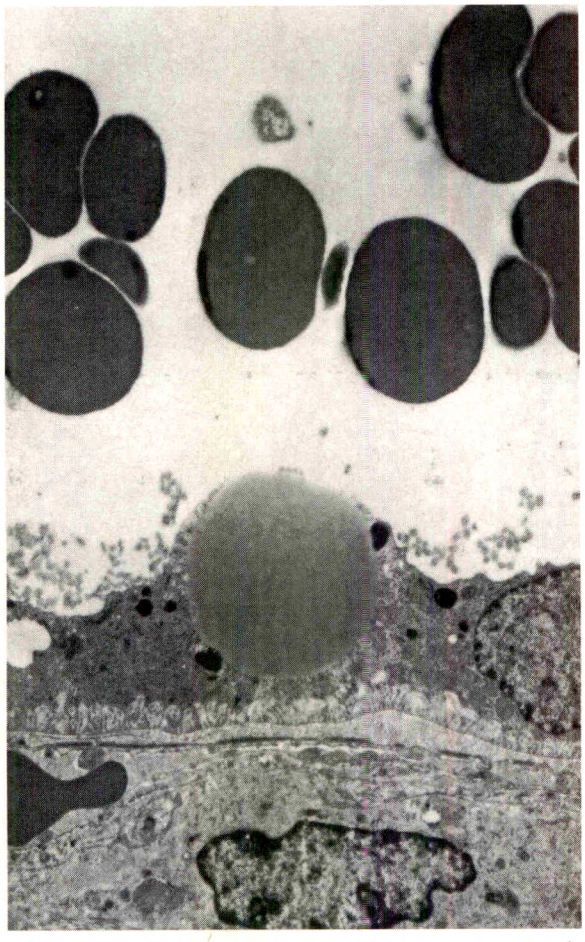


Fig. 5 (Lewis and associates). Electron micrograph of an eye seven days after injection of subretinal autologous blood (0.1 ml) followed by tissue plasminogen activator (25 μg/0.1 ml). The retinal pigment epithelium appears normal in all regions below the injection. A large lipid droplet characteristic of the normal retinal pigment epithelium is observed in the center of the figure. Numerous intact erythrocytes are observed in the subretinal space (× 1,800).

drainage of extensive subretinal hemorrhage may be beneficial in preventing retinal damage. To remove a subretinal hemorrhage, a cannulated subretinal fluid aspirator or an extrusion needle is passed through a pre-existing retinal break or a drainage retinotomy and into the subretinal space under the macular region.[13] Subretinal hemorrhages that are not clotted are frequently removed completely without mechanically damaging the overlying retina. In most cases, however, the subretinal hemorrhage is clotted, and the clot is tightly adherent to the neurosensory retina, retinal pigment epithelium, or choroid. Although a clot can be removed occasionally with a subretinal fluid aspirator, more often forceps are required, but even then the clot is frequently removed incompletely. Significant mechanical damage to the outer retina with shearing of the photoreceptors can occur while removing a subretinal clot. If the source of the subretinal hemorrhage is the choroid, clot removal can also cause further hemorrhage.[14] Other possible risks of clot removal include enlargement of the retinal break or drainage retinotomy with enlargement of the visual field defect and possible hemorrhage.[15]

An alternative approach to clear or assist in the surgical removal of subretinal hemorrhage is lysis of the fibrin clot within the subretinal space. Purified human tissue plasminogen activator produced by recombinant DNA technology is a clot-specific fibrinolytic agent that is currently available for use in patients. It has been shown to be effective in the clearance of postvitrectomy fibrin deposition, in the rapid resolution of experimental hyphema, in the resolution of experimentally induced retinal vascular occlusions, and in the clearing of experimentally produced vitreous hemorrhage.[5-11,16,17]

Tissue plasminogen activator is one of two kinds of plasminogen activators naturally occurring in many tissues in the body, particularly the blood. The regulation of tissue plasminogen activator is complex. Endothelial cells are able to release a preliminary type single chain, which when cleaved to tissue plasminogen activator is fibrin-selective and forms strong bonds with fibrin. Fibrin is the main component of a blood clot. The complex of tissue plasminogen activator and fibrin activates plasminogen into plasmin by hydrolyzing the arginine-valine bond of plasminogen. Plasmin, in turn, lyses fibrin, fibrinogen, and other procoagulant proteins, such as factors V, VIII, and XII, into soluble degradation products. The solubilization of fibrin destabilizes the clot and leads to the breakdown of the blood clot.[18]

Tissue plasminogen activator has advantages over other thrombolytic agents, such as streptokinase and urokinase, in that its activity is not only greatly enhanced in the presence of a fibrin clot, but the combination of fibrin, tissue plasminogen activator, and plasminogen forms a complex that sequesters the fibrinolytic reaction.[18,19] Tissue plasminogen activator is thus a fibrin-specific and therefore a clot-selective drug.[19] Also, urokinase and streptokinase have been shown to cause a large inflammatory response in the eye when used for vitreous hem-

orrhage and hyphema, and urokinase has been found to be toxic to the retina in high concentrations.[20]

Because of these reasons, tissue plasminogen activator is the most logical adjuvant to assist in cases where lysis of the subretinal blood clot is desired. We were interested not only in determining the efficacy of tissue plasminogen activator in clearing experimental subretinal hemorrhages, but we were also concerned with the possibility of retinal toxicity. A recent study showed that doses greater than 50 μg of tissue plasminogen activator injected intravitreally are toxic to the retina, and that the vehicle rather than the enzyme itself appears to be the toxic factor.[21] In contrast, clinical experience as well as other animal studies have shown that 25 μg of tissue plasminogen activator injected into the anterior chamber or vitreous cavity is not toxic to the retina.[5,7,10] Thus, it appears that there is a narrow margin of safety. Despite our injection into a smaller space as well as the direct contact between the tissue plasminogen activator and the photoreceptors, we did not find any morphologic toxic effect on the rabbit retina when tissue plasminogen activator was injected in the subretinal space at a dose of either 25 or 50 μg/0.1 ml. Additionally, there were no signs of inflammation, and the retina reattached without visible abnormalities. Since previous studies have shown that in the presence of fibrin the half life of intravitreal tissue plasminogen activator is doubled,[22] it is possible that the large amount of fibrin present in the subretinal clot decreased the amount of free tissue plasminogen activator available to cause toxic damage to the retina.

Our results indicate that the subretinal injection of 25 μg of tissue plasminogen activator is effective in accelerating the clearance of experimental subretinal hemorrhage when compared to either the natural course of experimental subretinal hemorrhage or the control. Our study also confirms the findings of Glatt and Machemer[3] of irreversible retinal damage within a day of a subretinal hemorrhage involving the macular region. Importantly, tissue plasminogen activator was found to decrease the damage to the overlying retina caused by the subretinal blood. Although we found that tissue plasminogen activator significantly accelerates the clearance of subretinal blood when compared to balanced salt solution, there were no differences in the morphologic appearance of the retina after the injection of either of them for the treatment of experimentally produced subretinal hemorrhage. This beneficial effect of both tissue plasminogen activator and balanced salt solution can probably be explained by the dilution of toxic factors released by the lysed blood cells, in consort with a reduction of the barrier to metabolic exchange posed by a contiguous blood clot in the subretinal or interphotoreceptor space.

Our results indicate that tissue plasminogen activator is safe and effective in promoting the clearance of experimentally produced subretinal hemorrhage. Although tissue plasminogen activator reduced the retinal damage caused by subretinal blood, a similar effect was observed with balanced salt solution, and neither of them prevented damage to the overlying retina completely. Further studies should evaluate the early intraoperative lysis of subretinal hemorrhage followed by surgical drainage of the unclotted blood.

References

1. Bennet, S. R., Blodi, C. F., and Folk, J. C.: Prognostic factors of visual outcome in patients with subretinal hemorrhage involving the fovea. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 153.

2. Hanscom, T. A., and Diddie, K. R.: Early surgical drainage of macular subretinal hemorrhages. Arch. Ophthalmol. 105:1722, 1987.

3. Glatt, H., and Machemer, R.: Experimental subretinal hemorrhage in rabbits. Am. J. Ophthalmol. 94:762, 1982.

4. Gilles, A., and Lahav, M.: Absorption of retinal and subretinal hemorrhages. Ann. Ophthalmol. 15:1068, 1983.

5. Lambrou, F. H., Snyder, R. W., Williams, G. A., and Lewandowski, M.: Treatment of experimental intravitreal fibrin with tissue plasminogen activator. Am. J. Ophthalmol. 104:619, 1987.

6. Snyder, R. W., Lambrou, F. H., and Williams, G. A.: Intraocular fibrinolysis with recombinant human tissue plasminogen activator. Arch. Ophthalmol. 105:1277, 1987.

7. Lambrou, F. H., Snyder, R. W., and Williams, G. A.: Use of tissue plasminogen activator in experimental hyphema. Arch. Ophthalmol. 105:995, 1987.

8. Jaffe, G. J., Lewis, H., Han, D. P., Williams, G. A., and Abrams, G. W.: Treatment of postvitrectomy fibrin pupillary block with tissue plasminogen activator. Am. J. Ophthalmol. 108:170, 1989.

9. Johnson, R. N., Olsen, K. R., and Hernandez, E.: Intravitreal tissue plasminogen activator treatment of experimental vitreous hemorrhage. Arch. Ophthalmol. 107:891, 1989.

10. Jaffe, G. J., Abrams, G. W., Williams, G. A., and Han, D. P.: Tissue plasminogen activator for postvitrectomy fibrin formation. Ophthalmology 97:184, 1990.

11. Williams, G. A., Lambrou, F. H., and Jaffe, G. J.: Treatment of postvitrectomy fibrin formation with intraocular tissue plasminogen activator. Arch. Ophthalmol. 106:1055, 1988.

12. Anderson, D. H., Stern, W. H., Fisher, S. K., Erickson, P. A., and Borgula, G.: Retinal detachments in the cat. The pigment epithelial photoreceptor interface. Invest. Ophthalmol. Vis. Sci. 7:906, 1983.

13. Flynn, H. W., Jr., Blumenkranz, M. S., Parel, J. M., and Lee, W. G.: Cannulated subretinal fluid aspirator for vitreoretinal microsurgery. Am. J. Ophthalmol. 103:106, 1987.

14. Abrams, G. W.: Retinotomies and retinectomies. In Ryan, S. J. (ed.): Retina, vol. 3. St. Louis, C. V. Mosby, 1989, pp. 321–322.

15. McDonald, R. H., Lewis, H., Aaberg, T. M., and Abrams, G. W.: Complications of endodrainage retinotomies created during vitreous surgery for complicated retinal detachment. Ophthalmology 96:358, 1989.

16. Vine, A. K., Maguire, P. T., Martonyi, C., and Kincaid, M. C.: Recombinant tissue plasminogen activator to lyse experimentally induced retinal arterial thrombi. Am. J. Ophthalmol. 105:266, 1988.

17. Oncel, M., Peyman, G. A., and Khoobehi, B.: Tissue plasminogen activator in the treatment of experimental retinal vein occlusion. Retina 9:1, 1989.

18. AHFS drug information. Bethesda, American Society of Hospital Pharmacy, 1989, p. 726.

19. Holyaerts, M., Rijken, O. C., Lijnen, H. R., and Collen, D.: Kinetics of the activation of plasminogen by human tissue plasminogen activator. Role of fibrin. J. Biol. Chem. 257:2912, 1982.

20. Koziol, J., Peyman, G. A., Sanders, D. R., Vlchek, J., and Goldberg, M. F.: Urokinase in experimental vitreous hemorrhage. Ophthalmic Surg. 6:79, 1975.

21. Johnson, M. W., Olsen, K. R., Hernandez, E., Irvine, W. D., and Johnson, R. N.: Retinal toxicity of recombinant tissue plasminogen activator in the rabbit. Arch. Ophthalmol. 108:259, 1990.

22. Jaffe, G. J., Green, G. D. J., McKay, B. S., Hartz, A., and Williams, G. A.: Intravitreal clearance of tissue plasminogen activator in the rabbit. Arch. Ophthalmol. 106:969, 1988.

OPHTHALMIC MINIATURE

She had intended to say, "Whose boy are you?" but she said nothing, her mouth opening on a vanished sentence. His eyes as they turned and looked down at her were the color of the lake just before dark when the last daylight has faded and the moon has not risen yet, and for an instant she thought she saw something fleeing across the surface of them, a lost light that came from nowhere and vanished into nothing.

Flannery O'Connor, *The Violent Bear It Away*
New York, Farrar, Straus & Cudahy, 1955, p. 156

The Prevalence of Retinal Vascular Abnormalities in Children and Adolescents With Essential Hypertension

Stephen R. Daniels, M.D., Matthew J. Lipman, M.D., Miles J. Burke, M.D., and Jennifer M. H. Loggie, M.D.

We studied 97 children and adolescents with essential hypertension by evaluating photographs of the optic fundus and fluorescein angiography. Photographs were examined for the presence of arteriolar narrowing, tortuosity, and arteriovenous nicking. Intraobserver and interobserver variability in determination of abnormalities was low with agreement of 75% for narrowing, 90% for tortuosity, and 100% for arteriovenous nicking. The prevalence of abnormalities was 41% (95% confidence interval, 31% to 50%) for arteriolar narrowing, 14% (95% confidence interval, 19% to 21%) for tortuosity, and 8% (95% confidence interval, 5% to 11%) for arteriovenous nicking. Of 97 patients, 50 (51%) had one or more abnormality. Retinal abnormalities are relatively common in young patients with essential hypertension.

THE ASSOCIATION between increased systemic blood pressure and hypertensive retinopathy has been known since the early 1900s. In 1939, Keith, Wagener, and Barker[1] were able to associate different grades of retinopathy with the prognosis of patients with hypertension. Although their findings dealt mostly with more severe forms of hypertension, subsequently Walsh[2] described the retinal vascular changes with less severe blood pressure increase in adults. Few studies have examined retinopathy in pediatric patients with hypertension. We investigated the prevalence of retinal vascular abnormalities in a population of children and adolescents with essential hypertension.

Accepted for publication Oct. 22, 1990.

From the Divisions of Cardiology (Dr. Daniels) and Clinical Pharmacology (Dr. Loggie), Departments of Pediatrics and Pediatric Ophthalmology (Dr. Burke), Children's Hospital Medical Center, Cincinnati, Ohio; and Department of Ophthalmology, University of Cincinnati, College of Medicine, Cincinnati, Ohio (Dr. Lipman). This study was supported in part by grants K08-HL01380, R01-HL34698, and RR-00123 from the National Institutes of Health. Dr. Daniels is an Established Investigator of the American Heart Association.

Reprint requests to Stephen R. Daniels, M.D., Division of Cardiology, Children's Hospital Medical Center, Elland & Bethesda Aves., Cincinnati, OH 45229.

Patients and Methods

We examined 97 children, aged 6 to 23 years, with systolic or diastolic blood pressure persistently greater than the 90th percentile for age and sex.[3] The subjects were patients in the Hypertension Clinic at the Children's Hospital Medical Center, Cincinnati, Ohio. Secondary causes of increased blood pressure were ruled out by standard clinical and laboratory examination. This study was approved by the Institutional Review Board for Research on Human Subjects of the Children's Hospital Medical Center.

After informed consent was obtained, ophthalmoscopic examination with photographs of the optic fundus and fluorescein angiography were performed by one of us (M.J.L.) according to the standard protocol of the clinical ophthalmology laboratory of the University of Cincinnati Hospital. Mydriatic ophthalmic eyedrops were administered to the subjects before examination. After dilation of the pupils, stereobiomicroscopy and indirect ophthalmoscopic examination were performed. Color and red-free retinal photographs were taken, followed by fluorescein angiography. The photographs of the optic fundus were examined for the presence of arteriolar narrowing, arteriovenous nicking, vascular tortuosity, exudates, and hemorrhages. The angiograms were examined for alterations of the permeability of the vascular bed. Arteriolar narrowing was defined as generalized narrowing of the arteriole when compared to the vein at an equivalent number

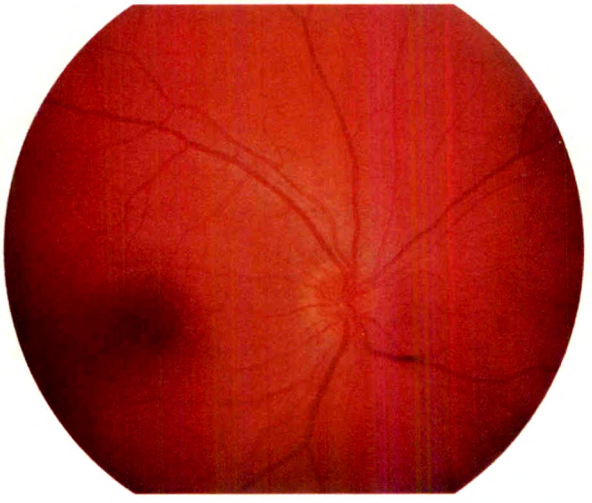


Fig. 1 (Daniels and associates). The mildest degree of arteriolar narrowing required to be considered abnormal.

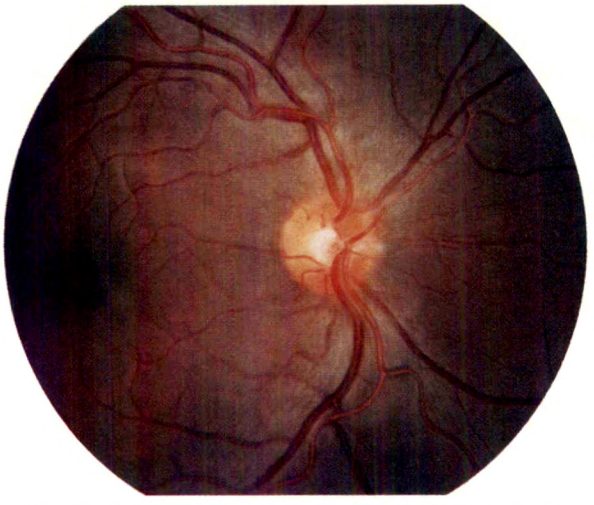


Fig. 2 (Daniels and associates). Retinal vascular abnormalities associated with hypertension, including arteriolar narrowing, vascular tortuosity, and arteriovenous crossing changes.

of bifurcations. To be considered abnormal, it was required that narrowing be present in at least two of the four quadrants (Fig. 1). Tortuosity was defined as three or more inflections of an artery or vein in the superotemporal or inferotemporal quadrants within 4 disk diameters of the optic disk. Arteriovenous nicking was present when any arteriovenous crossing abnormalities were present within 4 disk diameters around the optic disk. Arteriovenous crossings were evaluated for changes in the course of the vein, hiding of the venous blood column, and changes of color and size in the vein distal to the crossing.

Reproducibility in determination of abnormalities in photographs of the optic fundus was assessed by independent readings by two of us (M.J.L., M.J.B.). Twenty fundus photographs were assigned numbers and interpreted in a group by each of the two observers. Each observer read each photograph twice at separate sittings one week apart. The numbering was changed between readings so that the observers were unaware of the identity of the photograph or the previous interpretation. The reproducibility of detection of abnormalities was quantitated separately for arteriolar narrowing, tortuosity, and arteriovenous nicking by calculating the percent agreement and the kappa statistic[4] for repeated readings by a single observer and by separate observers.

Variables are presented as mean values ± standard deviation. The point prevalence was calculated for each of the retinal vascular abnormalities. A test-based 95% confidence interval was calculated for each prevalence.

The Student's *t*-test (for continuous variables) and chi-square analysis (for categorical variables) were used to determine if there were significant differences in age, race, sex, level of blood pressure, and duration of hypertension between patients with and without retinal vascular abnormalities. A level of $P < .05$ was used to determine statistical significance.

Results

The reproducibility for determination of retinal vascular abnormality was good both for a single observer making repeated measurements and for two observers. The within-observer reliability was 75% agreement for arteriolar narrowing (kappa = 0.50), 90% agreement for tortuosity (kappa = 0.81), and 100% agreement for arteriovenous nicking (kappa = 1.00). The between-observer reliability was 85% agreement for arteriolar narrowing (kappa = 0.57), 85% agreement for tortuosity (kappa = 0.60), and 100% agreement for arteriovenous nicking (kappa = 1.00).

Of the 97 patients, 48 were black and 49 were white. There were 24 females and 73 males. The average age of the patients was 14.7 ± 3.5 years. The average height was 165.2 ± 13.7 cm, and the average weight was 70.4 ± 20.5 kg. The

TABLE
PREVALENCE OF RETINAL VASCULAR ABNORMALITY BY RACE AND SEX

ABNORMALITY	BLACK FEMALES (12)	BLACK MALES (36)	WHITE FEMALES (12)	WHITE MALES (37)	TOTAL (97)
Arteriolar narrowing	6	14	4	16	40
Prevalence	0.50	0.39	0.33	0.43	0.41
95% C.I.	(0.22, 0.78)	(0.23, 0.55)	(0.06, 0.80)	(0.27, 0.59)	(0.31, 0.51)
Tortuosity	3	4	1	6	14
Prevalence	0.25	0.11	0.08	0.16	0.14
95% C.I.	(0.01, 0.49)	(0.00, 0.22)	(0.00, 0.23)	(0.04, 0.28)	(0.07, 0.21)
Arteriovenous nicking	0	5	0	3	8
Prevalence	0.00	0.14	0.00	0.08	0.08
95% C.I.	(0.00, 0.06)	(0.03, 0.25)	(0.00, 0.06)	(0.00, 0.17)	(0.05, 0.11)
Any abnormality	7	17	4	21	50
Prevalence	0.58	0.47	0.33	0.57	0.51
95% C.I.	(0.30, 0.86)	(0.32, 0.63)	(0.06, 0.60)	(0.41, 0.73)	(0.41, 0.61)

average duration of hypertension was 30.3 ± 31.1 months. Twenty-nine patients were taking antihypertensive medications and 68 were not taking medications.

Figure 2 presents a representative photograph of the optic fundus demonstrating arteriolar narrowing, tortuosity, and arteriovenous nicking. Of the 97 patients who had photographs taken of the optic fundus, 40 (41%; 95% confidence interval, 0.31% to 0.51%) had arteriolar narrowing, 14 (14%; 95% confidence interval, 0.07% to 0.21%) had tortuosity, and eight (8%; 95% confidence interval, 0.05% to 0.11%) had arteriovenous nicking. Six patients had both narrowing and tortuosity, two had both tortuosity and arteriovenous nicking, and one had all three abnormalities. Fluorescein angiography did not add information to that determined from the fundus photographs.

When the retinal vascular abnormalities are combined, 50 of 97 patients (51%; 95% confidence interval, 0.41% to 0.61%) had one or more abnormality. The prevalence of abnormality is presented by race and sex in the Table. There were no statistically significant differences in prevalence between the race and sex groups. There was also no statistically significant relationship between the level of systolic or diastolic blood pressure at the time of the study and the presence of retinopathy. Patients with retinal vascular abnormalities were significantly younger (13.9 compared with 15.6 years, P = .013) than patients without retinopathy. There was no significant difference in the known duration of hypertension between patients with and without abnormalities of the retinal vasculature.

Discussion

The reproducibility in the evaluation of retinal vascular abnormalities was reasonably good in this study, both for a single observer making repeated observations and between two observers. Kagan and associates[5] reported the results of three studies conducted by the World Health Organization on adults. They found that ophthalmologists were in general equal in precision to cardiologists and other physicians in evaluating photographs of the optic fundus. They reported intraobserver agreement ranging from 67% to 85% for generalized arteriolar narrowing, from 73% to 86% for irregularity in caliber or localized narrowing, and from 74% to 79% for changes at the arteriovenous crossing. Interobserver agreement ranged from 58% to 81% for generalized narrowing, from 63% to 80% for localized narrowing, and from 57% to 77% for changes at the arteriovenous crossing. The reliability was similar for routine ophthalmic examination, black-and-white photographs, or color slides. Our investigation demonstrated better reliability than that reported by Kagan and associates.[5] These results indicate that the determination of retinal abnormalities from photographs of the optic fun-

dus by skilled observers may be useful for study of the pediatric population.

Our findings suggest that early retinal vascular abnormalities are relatively common in pediatric patients. Van Buchem, Henvel-Aghina, and Henvel[6] found a prevalence of 6.2% for diffuse narrowing of the arterioles in adults aged 40 to 60 years with normal blood pressure. The prevalence for men with mild to moderate hypertension (systolic, 141 to 159 mm Hg; diastolic, 91 to 109 mm Hg) was 15.8%, and the prevalence for men with more severe hypertension (systolic, greater than 160 mm Hg; diastolic, greater than 110 mm Hg) was 30%. In that study, men with mild to moderate hypertension had a prevalence of changes at the arteriovenous crossings of 32.1%, whereas men with more severe hypertension had a prevalence of 35.3%. The prevalence of arteriovenous crossing changes increased with age. There was no relationship between age and diffuse arteriolar narrowing in the patients with hypertension.[6] The prevalence of markedly narrowed arterioles, however, was found to be a predictor of increased blood pressure in young subjects but not in older subjects.

Svardsrudd and associates[7] found that the frequency of arteriolar narrowing and arteriovenous crossing changes increased with higher systolic blood pressure in a sample of men 50 years of age. The prevalence of the abnormalities observed ranged from 40% at a systolic blood pressure of 140 mm Hg to 90% in patients with systolic blood pressure 190 mm Hg or greater. Comparable results were obtained for diastolic blood pressure with ocular findings more common at higher levels of pressure.

The finding in our study that patients with retinal vascular abnormalities were younger than those without abnormalities remains unexplained. Little is known about the timing and pathophysiologic characteristics of these abnormalities in children. Skalina and associates[8] have investigated the prevalence of ophthalmoscopic abnormalities in newborn infants with secondary hypertension. They found that 11 of 21 infants (52.3%) had one or more retinal vascular abnormality. This included a spectrum of abnormalities. All 11 patients had arteriolar narrowing, and three had abnormal tortuosity and nicking of the retinal vessels. They also described four infants with splinter hemorrhages, two with deeper blot-shaped hemorrhages, and two with retinal exudate. These findings, however, may not be relevant to older patient populations. For example, it is known that there are differences between premature infants and older individuals with respect to vascular fragility and response of blood vessels to increased blood pressure. None of our patients had evidence of retinal hemorrhage or exudate.

The prevalence of retinal vascular abnormalities observed in our pediatric population is similar to that in adults. The clinical significance of these findings, however, remains unknown. The observed changes are mild and had no effect on vision. Further longitudinal studies will be necessary to determine how these retinal vascular lesions progress over time in juveniles with essential hypertension and whether the abnormalities are of prognostic importance.

References

1. Keith, N. M., Wagener, H. P., and Barker, M. W.: Some different types of essential hypertension. Their course and prognosis. Am. J. Med. Sci. 197:332, 1939.

2. Walsh, J. B.: Hypertensive retinopathy description, classification, and prognosis. Ophthalmology 89:1127, 1982.

3. NHLBI Task Force on Blood Pressure Control in Children: Report of the Task Force on Blood Pressure Control in Children. Pediatrics 59:797, 1977.

4. Landis, J. R., and Koch, G. G.: The measurement of agreement for categorical data. Biometrics 33:159, 1977.

5. Kagan, A., Aurell, E., Dobree, J., Hara, K., McKendrick, C., Michaelson, I., Shaper, G., Sundaresan, T., and Tibblin, G.: A note on signs of the fundus oculi and arterial hypertension. Conventional assessment and significance. Bull. W.H.O. 34:955, 1966.

6. Van Buchem, F. S. P., Henvel-Aghina, J. W. M., and Henvel, J. E. A.: Hypertension and changes in fundus oculi. Acta Med. Scand. 176:539, 1964.

7. Svardsrudd, K., Wedel, H., Aurell, E., and Tibblin, G.: Hypertensive eye ground changes. Prevalence relation to blood pressure and prognostic importance. The study of men born in 1913. Acta Med. Scand. 204:159, 1978.

8. Skalina, M. E. L., Annable, W. L., Kliegman, R. M., and Fanaroff, A. A.: Hypertensive retinopathy in the newborn infant. J. Pediatr. 103:781, 1983.

Visual Recovery in Patients With Optic Neuritis and Visual Loss to No Light Perception

Thomas L. Slamovits, M.D., Carl E. Rosen, M.D., Kenneth P. Cheng, M.D., and Gerald G. Striph, M.D.

We reviewed the records of 151 patients with optic neuritis examined over an eight-year period. Of these patients, 12 developed visual acuity of no light perception during the first episode of optic neuritis in the affected eye. Eight of the 12 patients recovered visual acuity of 20/40 or better. Of these, five patients had visual acuity of 20/20 or better, one had visual acuity of 20/25, one had visual acuity of 20/30, and one had visual acuity of 20/40. Four of the 12 patients recovered peripheral visual fields but had dense central scotomas and visual acuity of less than 20/400. Dyschromatopsia persisted after visual recovery in 11 of 12 patients.

USEFUL VISUAL RECOVERY after the first episode of optic neuritis is the rule with improvement of visual acuity to 20/40 or better in 85% or more of patients.[1-10] It is not clear whether there is a similarly favorable prognosis for the subset of patients with optic neuritis with acute visual loss to no light perception. We studied 12 patients who developed visual acuity of no light perception during the first episode of optic neuritis in the affected eye.

Accepted for publication Oct. 29, 1990.

From the Departments of Ophthalmology (Drs. Slamovits and Rosen) and Neurology and Neurosurgery (Dr. Slamovits), Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; Department of Ophthalmology, Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, Pennsylvania (Dr. Cheng); and private practice, Toledo, Ohio (Dr. Striph).

This study was supported in part by an unrestricted departmental grant to the Department of Ophthalmology, Albert Einstein College of Medicine, Montefiore Medical Center from Research to Prevent Blindness, Inc.

Reprint requests to Thomas L. Slamovits, M.D., Department of Ophthalmology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 E. 210th St., Bronx, NY 10467.

Patients and Methods

We reviewed the records of 151 patients with optic neuritis, examined over an eight-year period, and found 15 patients who had acute visual loss to no light perception. Three patients were excluded either because previous episodes of optic neuritis were documented in the affected eye or because the patient's claim of no light perception visual acuity could not be substantiated reliably. The diagnosis of optic neuritis was made by accepted clinical standards.[2,9,11-14] Criteria for inclusion were the following: rapid onset of visual acuity loss to no light perception (over days); optic neuritis as the initial or only episode of visual loss in the acutely affected eye(s); swollen or normal optic nerve head on the affected side(s); absence of retinal lesions that might account for the visual deficit; and no history of congenital, toxic, infective, vascular, metabolic, or neoplastic etiologic factors that might confound diagnosis.

All patients had a complete ophthalmic examination by one of us (T.L.S.), which included a history, best-corrected visual acuity (Snellen charts, counting fingers, hand motions, or light perception), color vision testing with Ishihara plates, pupillary assessment, external and slit-lamp examination, applanation tonometry, and fundus examination with a dilated pupil. Subjective responses to pain on extraocular movements, red desaturation, and brightness desaturation were recorded. All patients also had visual field testing performed by certified ophthalmic technicians and thorough neurologic examinations performed by a neurologist.

Laboratory tests included blood cell count with differential, serum electrolytes, blood urea nitrogen, creatinine, glucose, urinalysis, rapid plasma reagin, VDRL, and fluorescent treponemal antibody absorption. Additionally, testing for autoimmune disease (erythrocyte sedimentation rate, antinuclear antibody, se-

rum complement, serum protein electrophoresis, rheumatoid factor, and lupus erythematosus preparations) and lumbar puncture (routine studies, oligoclonal banding, and myelin basic protein) were done when clinically indicated. Computed tomography of the head and orbits was performed on nine patients. Five of these patients also had magnetic resonance imaging studies.

Patients were told of the risks and possible benefits of corticosteroid therapy and that the effect of treatment on final visual outcome was not established. All received corticosteroid preparations either slightly before or shortly after visual acuity progressed to no light perception.

Repeat neuro-ophthalmic examinations were performed at frequent intervals as indicated by the patient's clinical course. All patients were followed up until visual acuity stabilized or recovery was considered complete. Duration of follow-up ranged from six to 87 months (mean, 21.2 months).

Results

Seven patients were female and five patients were male, ranging in age from 6 to 36 years. Three patients were younger than 18 years of age (Table).

The interval between onset of visual symptoms and the development of visual acuity of no light perception ranged from one to seven days, and the duration ranged from three to 14 days (Table). Acute visual loss to no light perception was unilateral in 11 patients (Cases 1 through 8 and 10 through 12) and simultaneously bilateral in one patient (Case 9). Bilateral simultaneous optic neuritis occurred in one patient (Case 10) who had unilateral visual acuity of no light perception.

Within two weeks, 11 of 12 patients showed improvement in visual acuity from no light perception, ranging from hand motions to 20/30. Seven patients (Cases 1, 3, 4, 8, 9, 10, and 12) recovered visual acuity of 20/40 or better within three months. Overall, eight of the 12 patients recovered visual acuity of 20/40 or better in the affected eye when last examined (five patients recovered visual acuity to 20/20 or better, one to 20/25, one to 20/30, and one to 20/40). Four patients (Cases 2, 5, 6, and 7) had visual acuity of counting fingers at the last examination (Table).

Follow-up visual field testing was performed in all 12 patients (Table). Four patients (Cases 2, 5, 6, and 7) had dense central scotomas involving the central 10 to 20 degrees at 34, 12, 22, and 12 months, respectively. One patient (Case 12) had a subtle central defect at three months, which fully recovered at five months. Two patients (Cases 1 and 11) had arcuate scotomas to the I_{2e} isopter on Goldmann perimetry at 13 and 16 months, respectively. Four patients (Cases 4, 8, 9, and 10) had normal visual fields at follow-up.

Seven of the eight patients without previous or subsequent episodes of optic neuritis had unilateral visual acuity loss to no light perception (Cases 1 through 4, 6, 7, and 12). One patient (Case 4) recovered visual acuity of 20/20 without a residual relative afferent pupillary defect. Of the six remaining patients with residual relative afferent pupillary defects three (Cases 1, 3, and 12) had return of visual acuity to 20/30 or better and had only slight residual relative afferent pupillary defects. The other three patients (Cases 2, 6, and 7) recovered visual acuity to counting fingers; these patients had obvious residual relative afferent pupillary defects. One patient (Case 9) had simultaneous bilateral visual acuity loss to no light perception and recovered visual acuity of 20/20 bilaterally without a residual relative afferent pupillary defect.

The remaining four patients had previous or subsequent episodes of optic neuritis in one or both eyes. Two patients (Cases 5 and 8) had one previous episode of optic neuritis each in the fellow eye. Two patients (Cases 10 and 11) had subsequent episodes of optic neuritis in both eyes. One patient (Case 8) recovered normal visual acuity, brisk pupillary responses bilaterally, and did not have any relative afferent pupillary defect. Three patients (Cases 5, 10, and 11) were left with bilaterally sluggish direct pupillary responses and either no relative afferent pupillary defect or a subtle relative afferent pupillary defect on the side with the more profound visual acuity or field loss.

Six of the eight patients with optic neuritis and visual acuity of no light perception (Cases 2, 3, 4, 6, 7, and 12) without previous or subsequent episodes of optic neuritis continued to report subjective red desaturation in their affected eye as compared to their unaffected eye. One patient (Case 1) did not note subjective red desaturation; however, this patient was only able to identify five of 12 Ishihara color plates correctly with the affected eye.

TABLE
VISUAL VARIABLES IN PATIENTS WITH OPTIC NEURITIS AND VISUAL LOSS TO NO LIGHT PERCEPTION*

CASE NO. AGE (YRS), SEX	ONSET TO NLP (DAYS)	DURATION OF NLP (DAYS)	VISUAL ACUITY 2 WEEKS	VISUAL ACUITY 3 MONTHS	VISUAL ACUITY LAST EXAMINATION	FOLLOW-UP PERIOD (MOS)	VISUAL FIELD SCOTOMA AT LAST EXAMINATION	DIAGNOSIS AT LAST EXAMINATION
1, 10, F	4	3	CF 4 ft	20/40	20/25	13	I2c isopter	Optic neuritis
2, 36, F	6	7	HM	CF 4 ft	CF 4 ft	34	Central 10 degrees	Probable multiple sclerosis
3, 26, F	1	12	CF 2 ft	20/30	20/20	10	—	Multiple sclerosis
4, 16, F	3	5	CF 6 ft	20/20	20/20	6	Full	Optic neuritis
5, 34, M	2	13	HM	CF 8 ft	CF 6 ft	12	Central 20 degrees	Multiple sclerosis
6, 31, F	3	7	HM	CF 8 ft	CF 6 ft	22	Central 10 degrees	Optic neuritis
7, 30, F	6	5	CF	CF 3 ft	CF 3 ft	12	Central 20 degrees	Multiple sclerosis
8, 28, M	6	4	20/200	20/25	20/15	16	Full	Multiple sclerosis
9, 17, F†	7	10	HM	20/25	20/20	10	Full	Probable lupus erythematosus
10, 6, M	5	4	CF 2 ft	20/30	20/30	87	Full	Optic neuritis
11, 32, F	4	14	NLP	20/100	20/40	16	I2c isopter	Probable lupus erythematosus
12, 29, M	3	3	20/30	20/30	20/20	16	Full	Optic neuritis

*HM indicates hand motions; CF indicates counting fingers; and NLP indicates no light perception.

†Patient 9 had simultaneous bilateral visual acuity loss to no light perception with full recovery of visual acuity and visual field in both eyes.

Only three patients (Cases 4, 8, and 9) recovered visual acuity sufficiently to identify all Ishihara color plates correctly; all three had visual acuity of 20/20 or better. Two of these patients (Cases 4 and 8) continued to report subjective red desaturation. Three patients (Cases 2, 5, and 7) were unable to identify any Ishihara color plates correctly and all demonstrated dense central scotomas with visual acuity of counting fingers.

At initial manifestation, multiple sclerosis was diagnosed in one patient (Case 5), and based on neurological examination and clinical symptomatology multiple sclerosis was suspected in five patients (Cases 2, 3, 7, 8, and 9; Table). Three of these five patients developed definite multiple sclerosis over the follow-up period (Cases 3, 7, and 8). Although two patients (Cases 9 and 11) were not given definitive diagnoses, seropositive systemic lupus erythematosus and seronegative systemic lupus erythematosus were suspected, respectively. Five patients continued to have the diagnosis of idiopathic optic neuritis (Cases 1, 4, 6, 10, and 12; Table) over the entire follow-up period.

One patient (Case 5) had a previous episode of optic neuritis with visual acuity of no light perception in the fellow eye two years before this episode, which had left him with a dense central scotoma and visual acuity of counting fingers. One patient (Case 8) had an episode of optic neuritis with visual acuity loss to no light perception in the fellow eye six years before this episode with recovery of visual acuity to 20/15. One patient (Case 10) had five subsequent recurrences of optic neuritis, twice in the affected eye and three times in the fellow eye. During the second recurrence in the fellow eye, visual acuity decreased to no light perception. On all occasions, visual acuity returned to 20/30. One patient (Case 11), three months after the initial episode, had involvement of the fellow eye to no light perception with visual acuity recovery to 20/30 at last examination, followed by a recurrence in the affected eye to counting fingers with good visual acuity recovery at last examination to 20/40.

All 12 patients had pain on movement of the eye. Two patients reported paresthesias of the extremities and one patient had Lhermitte's

sign. Phosphenes were not described. Nine of the 12 patients had retrobulbar optic neuritis, with a bilateral manifestation in one patient (Case 9). Three patients demonstrated anterior optic neuritis with papillitis (Cases 6, 10, and 11).

Nine patients had computed tomography of the head and orbits. Four patients (Cases 1, 2, 4, and 5) had normal results of the studies, whereas five patients (Cases 6, 7, 9, 10, and 11) had abnormal results of the scans. The studies of one patient (Case 7) disclosed normal appearing optic nerves with an area of slightly decreased attenuation in the cerebellar peduncles. Two patients (Cases 6 and 11) demonstrated unilateral thickening of the optic nerve, whereas two patients (Cases 9 and 10) showed bilateral optic nerve thickening.

Magnetic resonance imaging scans were performed on five patients. Three studies (Cases 6, 10, and 12) had normal results. One patient (Case 7) had periventricular and supraventricular plaques, and one patient (Case 9) had a thickened chiasm that returned to normal size on follow-up scans.

Discussion

In a 15-year study of optic neuritis, Carroll[1] examined 240 patients with optic neuritis and described seven patients with visual acuity loss to no light perception in one or both eyes. Five of these seven patients recovered visual acuity of 20/40 or better in at least one eye. Of 172 patients with optic neuritis, Perkin and Rose[2] described six patients with visual acuity of no light perception; three of the six patients demonstrated visual acuity recovery to 20/20 within six weeks.

Earl and Martin[4] reviewed the records of 104 patients with optic neuritis of recent onset and concluded that the prognosis for visual recovery was better in patients under 45 years of age than in those older than this age. Initial visual loss was also a prognostic factor in the group older than 45 years of age. Of the five patients over 45 years of age whose vision did not recover, four had initial visual acuity of counting fingers or less.

Cohen, Lessell, and Wolf,[3] in a study of the risks of developing multiple sclerosis after an episode of optic neuritis, described 60 patients after the initial manifestation of optic neuritis. Their study suggests a worse visual prognosis for an initial manifestation of optic neuritis with less than 20/200 visual acuity. Thirteen patients with initial visual acuity of 20/40 or better all recovered visual acuity of 20/20 or better; of 23 patients with initial visual acuity between 20/50 and 20/200, 22 recovered visual acuity of 20/40 or better; of 24 patients with initial visual acuity worse than 20/200 (of which three were no light perception), visual acuity remained at that level in nine patients, one patient recovered visual acuity to 20/50, and 14 patients recovered visual acuity of 20/20 or better. The outcome of the patients with visual acuity of no light perception was not specifically stated.

Eight of our 12 patients (67%) had recovery of visual acuity to better than 20/40 within three months (Table). This was not significantly different from those studies that considered all degrees of acute visual loss in optic neuritis.[2,5,6,8-10] Nikoskelainen[6] treated 176 patients with optic neuritis for at least six months and reported a 69% recovery to visual acuity of 20/30 or better in 133 eyes after their initial episode. Bradley and Whitty[9] reported that 53 of their 71 patients (75%) had 20/25 or better visual acuity at six months after an initial episode. Beck and associates[10] reported that 24 of 32 eyes with unilateral optic neuritis recovered visual acuity to 20/25 (it was not stated if this group included subsequent or previous manifestations of optic neuritis). Our review of published reports suggests that 50% to 71% of patients who have had optic neuritis with visual acuity of no light perception recover visual acuity of 20/40 or better. Excluding the two patients possibly attributable to systemic lupus erythematosus, the visual acuity recovery rate to 20/40 or better within three months was 60% for the ten patients with optic neuritis assumed to be related to a process of either disseminated demyelination (multiple sclerosis) or of focal, isolated demyelination (idiopathic optic neuritis) (Table).

Two of our patients developed additional occurrences of optic neuritis during follow-up. In one patient, visual acuity of no light perception occurred in the contralateral eye. In the other patient, recurrences were bilateral, including visual acuity of no light perception in the contralateral eye. Both patients had good visual recovery. This is in contrast to Lynn[15] who reported that subsequent episodes of optic neuritis adversely affect visual recovery after finding that only eight of 33 patients (24%)

with recurrent optic neuritis attained visual acuity of better than 20/30. Both Nikoskelainen[6] and Perkin and Rose[2] similarly reported a less favorable outcome for patients with recurrent optic neuritis, reporting visual acuity recovery to 20/30 or better in 54% and 57% of their patients, respectively. In the acute phase, visual acuity of no light perception persisted for three to 14 days (mean, 6.9 days) in the eight patients in whom visual acuity recovered to 20/40 or better (Table). Visual acuity of no light perception persisted for five to 13 days (mean, 8.0 days) for the four patients in whom visual acuity recovered to counting fingers (Table).

All three of our patients younger than 18 years of age recovered visual acuity to 20/30 or better (Table). Kriss and associates[5] described 39 children with optic neuritis and found 53 of 68 eyes examined (78%) recovered visual acuity to 20/20 or better (the number of patients with visual acuity of no light perception was not stated). Farris and Pickard[16] described six children with simultaneous, bilateral optic neuritis, all of whom were treated with intravenous methylprednisolone. All patients had severe visual loss, four to no light perception. Five patients recovered visual acuity to 20/25 or better, and one patient who recovered visual acuity to 20/40 was lost to follow-up. Since our patients were all younger than 36 years of age, we did not have the opportunity to address any potential differences in outcome related to age as reported by Earl and Martin.[4]

Many investigators have assessed pupillary reactions in patients with optic neuritis[17,18] and have found good recovery of visual acuity with concomitant residual relative afferent pupillary defects. Burde and Gallin[19] examined nine patients with recovered retrobulbar optic neuritis with visual acuity of at least 20/30 and found relative afferent pupillary defects in all during the acute phase, whereas five patients had chronic relative afferent pupillary defects. Cox, Thompson, and Corbett[17] found the pupillary defect in acute optic neuritis worsened as visual acuity decreased and improved as vision recovered. Our findings agree with those of Cox, Thompson, and Corbett,[17] in that six of our seven patients with a single unilateral episode of optic neuritis and visual acuity loss of no light perception were left with a residual relative afferent pupillary defect.

Color vision abnormalities have been reported in 50% to 100% of patients with resolved optic neuritis.[2,15,19,20] Testing procedures in these studies included the Farnsworth-Munsell 100-hue color test, Ishihara color plates, and pseudoisochromatic color plates. Six of the eight patients with no previous or subsequent recurrences of optic neuritis reported subjective red desaturation in their affected eyes, including two patients who correctly identified all of the Ishihara color plates. Overall, dyschromatopsia was identified in 11 of our 12 patients (92%).

It is believed that treatment with corticosteroids shortens the duration of symptoms in acute optic neuritis. All of our patients were treated with corticosteroids, most with high doses of intravenous methylprednisolone and subsequent oral taper, yet no significant conclusions can be drawn from our study regarding any benefit of corticosteroid therapy on eventual visual outcome. The ongoing multicenter Optic Neuritis Treatment Trial may provide information regarding the effect of corticosteroid treatment on visual prognosis for patients with optic neuritis and perhaps even on the subset of patients with visual acuity of no light perception and optic neuritis.

References

1. Carroll, F. D.: Optic neuritis. A 15-year study. Am. J. Ophthalmol. 35:75, 1952.

2. Perkin, G. D., and Rose, F. C.: Optic Neuritis and Its Differential Diagnosis. Oxford, Oxford Medical Publications, 1979, pp. 91–101.

3. Cohen, M. M., Lessell, S., and Wolf, I. A.: A prospective study of the risk of developing multiple sclerosis in uncomplicated optic neuritis. Neurology 29:208, 1979.

4. Earl, C. J., and Martin, B.: Prognosis in optic neuritis related to age. Lancet 1:74, 1967.

5. Kriss, A. K., Francis, D. A., Cuendet, F., Halliday, A. M., Taylor, D. S. I., Wilson, J., Keast-Butler, J., Batchelor, J. R., and McDonald, W. I.: Recovery after optic neuritis in childhood. J. Neurol. Neurosurg. Psychiatry 51:1253, 1988.

6. Nikoskelainen, E.: Later course and prognosis of optic neuritis. Acta Ophthalmol. 53:273, 1975.

7. Rucker, C. W.: Optic neuritis of unknown etiology. Trans. Am. Acad. Ophthalmol. Otolaryngol. 60:93, 1956.

8. Rawson, M. D., and Liversedge, L. A.: Treatment of acute retrobulbar neuritis and corticotrophin. Lancet 2:1044, 1966.

9. Bradley, W. G., and Whitty, C. M.: Acute optic neuritis. Its clinical features and their relation to the prognosis for the recovery of vision. J. Neurol. Neurosurg. Psychiatry 30:531, 1967.

10. Beck, R. W., Ruchman, M., Savino, P., and Schatz, N.: Contrast sensitivity measurements in acute and resolved optic neuritis. Br. J. Ophthalmol. 68:756, 1984.

11. Nikoskelainen, E.: Symptoms, signs and early course of optic neuritis. Acta Ophthalmol. 53:254, 1975.

12. Miller, N. R. (ed.): Walsh and Hoyt's Clinical Neuro-Ophthalmology, ed. 4, vol. 1. Baltimore, Williams and Wilkins, 1982, pp. 227–248.

13. Wray, S. J.: Optic neuritis. In Lessell, S., and Van Dalen, J. T. W. (eds.): Neuro-Ophthalmology. Amsterdam, Excerpta Medica, 1980, pp. 18–30.

14. Matthews, W. B., Acheson, E. D., Batchelor, J. R., and Weller, R. O. (eds.): McAlpine's Multiple Sclerosis. Edinburgh, Churchill Livingstone, 1985.

15. Lynn, B. H.: Retrobulbar neuritis. A survey of the present condition of cases occurring over the last fifty-six years. Trans. Ophthalmol. Soc. U.K. 79:701, 1959.

16. Farris, B. K., and Pickard, D. J.: Bilateral postinfectious optic neuritis and intravenous steroid therapy in children. Ophthalmology 97:339, 1990.

17. Cox, T. A., Thompson, H. S., and Corbett, J. J.: Relative afferent pupillary defects in optic neuritis. Am. J. Ophthalmol. 92:685, 1981.

18. Bynke, H., Rosen, I., and Sandberg-Wolheim, M.: Correlation of visual evoked potentials, ophthalmological and neurological findings after unilateral optic neuritis. Acta Ophthalmol. 58:673, 1980.

19. Burde, R. M., and Gallin, P. F.: Visual parameters associated with recovered retrobulbar optic neuritis. Am. J. Ophthalmol. 79:1034, 1975.

20. Griffin, J. F., and Wray, S. H.: Acquired color vision defects in retrobulbar neuritis. Am. J. Ophthalmol. 86:193, 1978.

OPHTHALMIC MINIATURE

I pressed him hard and threatened him until he prostrated himself before me, saying, "Spare my life, lord, for I have faithfully served Egypt all my days and in the name of Egypt have tortured prisoners and stolen their food. But this spy is no ordinary man. His tongue is strange and whistles like a nightingale and he has promised me great wealth if I will feed him and keep him alive until the coming of Horemheb. He has also promised to restore my sight, having been blind himself until a great physician healed his one eye. He has promised to bring me to this great physician that my sight also may be restored and that I may live in the city among my fellows and enjoy my wealth."

Mika Waltari, *The Egyptian*
Helsinki, WSOY, 1983, p. 442

Acetazolamide in the Treatment of Abnormal Oculovestibular Response

Ralph B. Hester III, M.D., and Bradley K. Farris, M.D.

We treated seven patients with incapacitating vertigo elicited by walking down a grocery store aisle or driving a car. Results of neurologic, neuro-ophthalmic, and neuroradiologic examinations were normal. Episodic vertigo secondary to an abnormal oculovestibular response was diagnosed. Each patient was given a trial of 250 to 500 mg of acetazolamide daily. Symptoms resolved completely in four patients, two patients had near resolution of symptoms, and one patient had no relief. Carbonic anhydrase activity has been demonstrated in the inner ear, and acetazolamide has been shown to affect the ion balance of the inner ear fluids.

In 1988, Meyerhoff[1] described a series of patients who had episodic vertigo triggered by optokinetic stimuli. Vertigo secondary to an abnormal oculovestibular response was diagnosed, presumably associated with Ménière's disease.

We treated seven patients between 1986 and 1989 who had episodic vertigo triggered by optokinetic stimuli in their visual periphery. Each patient described vertigo elicited by walking down a grocery store aisle or driving a car. Nothing was found on examination of these patients that could account for their symptoms. In 1979, Donat and Auger[2] described the successful use of acetazolamide in the treatment of periodic ataxia. Prompted by this report, we treated our patients with acetazolamide. The symptoms in six of seven patients improved.

Accepted for publication Oct. 23, 1990.

From the Department of Ophthalmology, Dean A. McGee Eye Institute, University of Oklahoma College of Medicine, Oklahoma City, Oklahoma.

Reprint requests to Bradley K. Farris, M.D., 608 Stanton L. Young Blvd., Oklahoma City, OK 73104.

Case Reports

Case 1

A 32-year-old woman had intermittent episodes of vertigo for one year. On further questioning, the patient stated that her actual problem was with passing objects in her visual periphery; she could not walk down a grocery store aisle without becoming dizzy. Results of otolaryngologic and gynecologic examinations were normal. Her medical history was significant only for migraine.

Neuro-ophthalmic examination on Aug. 1, 1986, showed best-corrected visual acuity of 20/20 in each eye. The refractive error was minimal. The patient was orthophoric at both near and distance. A fine horizontal nystagmus was present in primary gaze and upgaze, worsening in gaze right or left. The nystagmus dampened on convergence, typical for congenital nystagmus. Optokinetic nystagmus and results of the neurologic examination were normal. A magnetic resonance image of the brain was normal. Acetazolamide, 250 mg, twice daily was initiated.

Examination six weeks later disclosed that the episodes of vertigo had decreased markedly. Results of the neuro-ophthalmic examination were unchanged. The symptoms continued to improve, and the patient has refused a dosage reduction since, remaining symptom-free.

Case 2

A 35-year-old woman had blurred vision and headaches for eight months. The patient further described a feeling of discomfort, with dizziness and nausea, caused by environmental motion. The symptoms were triggered when walking down a grocery store aisle or when viewing moving cars and road lines while driving. Results of previous ophthalmic and neurologic examinations were normal. A magnetic resonance image of the brain was normal. A

neuro-otolaryngologist thought her symptoms were functional.

Neuro-ophthalmic examination on Aug. 12, 1986, showed best-corrected visual acuity of 20/20 in each eye. The refractive error was minimal. The patient was orthophoric both at near and at distance. Results of the remainder of the examination, including optokinetic nystagmus, were normal. A regimen of 125 mg of acetazolamide twice daily was initiated.

With minimal relief after six weeks, the patient sought another opinion from a neurologist and an otolaryngologist. They agreed she was motion-sensitive but found no abnormalities on examination. The acetazolamide was restarted at the same dosage, and two weeks later she noted significant improvement. The dosage was increased to 250 mg twice daily with further improvement. When examined one year later, the patient was taking 375 mg of acetazolamide a day with complete resolution of the symptoms. She has refused to taper the dosage.

Case 3

For ten years, a 42-year-old woman had dizziness, worsened by ocular movements, and intermittent blurred vision while reading. At age 31 years, the patient noted that walking down hallways and through tunnels made her dizzy. This progressed to the point where she was unable to walk down a grocery store aisle or drive a car without having incapacitating vertigo. Results of previous ophthalmic, neurologic, and otolaryngologic examinations were normal. One physician believed her complaints were functional. Medications included 10 mg of propranolol hydrochloride daily and diazepam as needed.

Neuro-ophthalmic examination on Sept. 9, 1987, showed best-corrected visual acuity of 20/20 in each eye. The patient had moderate myopia in each eye. She was orthophoric both at near and at distance. The patient was noted to have minimal rotary nystagmus when looking down and right and down and left. Optokinetic nystagmus was normal, although it did trigger the symptoms. A magnetic resonance image of the brain was normal. A course of 125 mg of acetazolamide twice daily was initiated.

Examination eight weeks later disclosed that her symptoms were improved markedly. On May 24, 1988, the patient had no complaints, was symptom-free, and results of an examination were normal. She has refused tapering of the dosage.

Case 4

A 32-year-old man had dazed vision for six months. The patient stated that he had difficulty watching rapidly moving objects, and walking down an aisle in a grocery store caused dizziness and blurred vision. The patient also had difficulty distinguishing objects as they moved beside him. He was taking diazepam intermittently, which seemed to help somewhat. He was examined by a neurologist, with normal results of an examination. An otolaryngologist suspected the patient had a viral vestibulitis.

Neuro-ophthalmic examination on April 20, 1988, showed best-corrected visual acuity of 20/15 in each eye. The patient had no refractive error. He was orthophoric at near, with a small comitant esophoria at distance. The patient had no nystagmus and normal optokinetic nystagmus. A magnetic resonance image of the brain was normal. A course of 125 mg of acetazolamide twice daily was initiated.

Examination nine weeks later disclosed that the patient had no significant improvement while taking the acetazolamide. Because of the moderate relief from taking the diazepam, he refused to try an increased dose of acetazolamide, and this was discontinued. Three months later, the patient stated that he was reasonably comfortable while taking diazepam.

Case 5

A 37-year-old woman had intermittent vertigo and blurred vision for three years. The patient stated that three years previously she awoke with dizziness and blurred vision. Her persistent dizziness gradually improved, although the patient continued to have vertigo with nausea and vomiting when walking down a grocery store aisle. Results of an otolaryngologic examination were normal. A magnetic resonance image of the brain was normal. In September 1987, a neurologist diagnosed posterior occipital headaches and radiculopathy in the left arm. A computed tomographic scan of the brain was normal, and she was given a trial of prednisone for presumed multiple sclerosis. No symptomatic improvement was noted.

Neuro-ophthalmic examination on Jan. 18, 1989, showed best-corrected visual acuity of 20/15 in each eye. The refractive error was minimal. She was orthophoric both at near and at distance. The patient had no nystagmus. Optokinetic nystagmus was normal, although it did trigger the symptoms. A regimen of 125 mg of acetazolamide twice daily was initiated.

Examination two weeks later disclosed that the patient had had considerable subjective improvement. On March 14, 1989, the patient stated that her dizziness had resolved completely, and she refused tapering of the original dosage of 125 mg twice daily.

Case 6

A 39-year-old man had intermittent dizziness, which he attributed to a closed head injury with skull fracture and brief loss of consciousness he had sustained 15 years previously. In February 1989, he fell at work, again sustaining a mild closed head injury with brief loss of consciousness. The patient had persistent dizziness thereafter. He stated that patterns on wallpaper and peripheral motion while driving triggered the dizziness and nausea. Results of an ophthalmic examination were normal. A magnetic resonance image of the brain was also normal.

Neuro-ophthalmic examination on April 4, 1989, showed best-corrected visual acuity of 20/15 in each eye. The patient had mild myopia and astigmatism with the rule in each eye. He was orthophoric both at near and at distance. The patient had no nystagmus and optokinetic nystagmus was normal. Results of the neurologic examination were normal. He was given 125 mg of acetazolamide once daily.

Examination four weeks later disclosed marked subjective improvement. Because of some persistent mild episodes, the dosage was increased to 250 mg once daily. One month later, the patient stated that the dosage increase resulted in further improvement in his tolerance of motion. He has refused a trial of dosage reduction.

Case 7

A 47-year-old man had difficulty driving for four years. The patient had intermittent episodes of aberration of his peripheral vision while driving. The symptoms were triggered when cars or the landscape would pass by him rapidly in his periphery. The patient was no longer able to go grocery shopping because of incapacitating vertigo when walking down the aisles and was no longer comfortable in crowds because of the same problem with people moving past him. A magnetic resonance image of the brain demonstrated a calcified mass in the pineal region, believed to be benign and unrelated to the symptoms.

Neuro-ophthalmic examination on Oct. 11, 1989, showed best-corrected visual acuity of 20/20 in each eye. The refractive error was minimal. He was orthophoric both at near and at distance. The patient had no nystagmus and normal optokinetic nystagmus. Results of a neurologic examination were normal. There was no upgaze paresis, retraction nystagmus, or pupillary abnormalities. Acetazolamide, 125 mg, once daily was initiated.

Examination three months later disclosed that the patient had initially noted a definite improvement on the acetazolamide. A drunken episode, however, resulted in worsening of the symptoms. The dosage was increased to 125 mg twice daily, and the patient was encouraged to limit his alcohol intake. Three weeks later, he stated that the symptoms had nearly resolved. He has refused any reduction in the dosage.

Results

Four of the patients we treated were women and three were men with an average age of 38 years (range, 32 to 47 years). The duration of symptoms varied from six months to 15 years. Five of our patients had been symptomatic for one year or longer.

Since there were no findings on examination to suggest an origin, each patient had been examined by several physicians; ophthalmologists, otolaryngologists, and neurologists were the specialists most frequently consulted. All but two of the patients (Cases 6 and 7) underwent an extensive examination by an otolaryngologist with normal results of a neurotologic examination. Ménière's disease was not suspected in any of the patients. Two patients were told their complaints were functional in nature (Cases 2 and 3). One patient (Case 4) was suspected of having a viral vestibulitis, and another patient (Case 5) was presumed to have multiple sclerosis.

Each patient had a unique set of symptoms. Dizziness and blurred vision were frequent complaints. In several patients, it was only with further questioning that the true problem was ascertained. Optokinetic stimuli, usually in the form of telephone poles or other cars seen peripherally while driving or items on the shelves at the grocery store seen while walking down the aisle, would cause symptoms ranging from light-headedness to true vertigo with nausea and vomiting.

All seven patients had normal results of neurologic and neuro-ophthalmic examinations,

except for the finding of minimal nystagmus in two patients (Cases 1 and 3). All of the patients had normal optokinetic nystagmus testing. In two patients (Cases 3 and 5), viewing the optokinetic flag was enough of a stimulus to trigger the symptoms. Each patient was orthophoric for both near and distant vision, with the exception of one (Case 4). All seven patients had normal ocular motility. Each patient underwent magnetic resonance imaging to rule out the possibility of a posterior fossa lesion. The magnetic resonance image in one patient (Case 7) demonstrated a calcified mass in the pineal region. This was believed to be unrelated to his symptoms.

The patient in Case 1 was initially given a relatively large dosage of acetazolamide, 500 mg a day. Four patients (Cases 2 through 5) were initially given 250 mg a day. As we gained experience, we learned to minimize the side effects. Thus, our last two patients (Cases 6 and 7) were initially given 125 mg a day and then had the dosage increased as necessary. In four of the patients the condition stabilized on a dosage of 250 mg a day, whereas two patients continued to be given a higher dosage. Although acetazolamide has the potential to cause numerous side effects,[3,4] our patients only had extremity paresthesias, mild fatigue, and altered taste, all of which resolved a few weeks after initiation of therapy.

Because no objective evidence of disease was found on examination of these patients, there was no objective means of documenting improvement. Subjectively, however, our patients reported dramatic improvement in their symptoms. The improvement while taking acetazolamide was gradual. All of our patients except two (Cases 2 and 4) noticed a slight improvement in their tolerance of motion within the first week and were improved markedly on their first follow-up visit. The symptoms of the patient in Case 2 were slow to improve with acetazolamide, and it was discontinued after a six-week trial. On a second trial at the same dosage, the symptoms improved dramatically. This was believed to be the result of better compliance. The symptoms in only one patient (Case 4) did not improve while taking acetazolamide. This patient had satisfactory relief while taking diazepam and chose to continue rather than try an increased dosage of acetazolamide. An important aspect in the treatment of these patients was our emphasis to them that the improvement was gradual, and it might take several weeks before significant improvement was noted. Four of our patients have remained asymptomatic, and two patients have had near resolution of their symptoms. These six patients have refused tapering of their dosage of acetazolamide.

Discussion

Our patients appear to have episodic vertigo triggered by optokinetic stimuli in their peripheral vision. This abnormal oculovestibular response represents a disturbance in the vestibular system. It has been seen in patients with Ménière's disease and has been successfully treated with vestibular nerve section.[1] We do not believe that our patients have classic Ménière's disease or the vestibular form of Ménière's disease, because they denied the symptoms of tinnitus, aural pressure or fullness, and fluctuating hearing loss associated with the episodes of vertigo.[5] Although no objective evidence of vestibular dysfunction was found on examination of these patients, we believe they have a subtle disturbance of the peripheral vestibular system, possibly involving the fluids of the inner ear. Acetazolamide, the prototype of a class of agents that act to inhibit the enzyme carbonic anhydrase reversibly, was successful in treating our patients and has been shown to have an effect on inner ear fluids.

Acetazolamide produces a modest diuresis, initial kaliuresis, a decrease in the concentration of bicarbonate in the extracellular fluid, and a metabolic acidosis.[6] Although the diuretic effect of the drug is self-limiting because of its production of a metabolic acidosis, it has proven to be of therapeutic benefit in various other conditions.[2,7-15] The discovery that acetazolamide was beneficial in the treatment of hereditary paroxysmal ataxia was serendipitous in that periodic paralysis was misdiagnosed in a patient with this disorder.[15] The symptoms of the patient improved on the acetazolamide. As a result, Donat and Auger[2] successfully used acetazolamide in the treatment of a mother and son with familial periodic ataxia; the patients had almost complete elimination of their episodic attacks of cerebellar incoordination and vertigo. It was this report that prompted us to use acetazolamide in the treatment of our patients.

Vestibular perilymph, primarily derived from plasma[16] and having a chemical composition

resembling a plasma ultrafiltrate, is the precursor of endolymph.[17-19] Endolymph has a characteristically high potassium concentration,[20,21] and a chemical (potassium and sodium) gradient exists between endolymph and perilymph producing a transepithelial potential between these fluids.[22,23] This exposes the hair-bearing ends of the sensory hair cells to anodal polarization. A high potassium concentration in the presence of anodal polarization renders the membrane of excitable cells more sensitive to mechanical deformation.[24] This suggests that maintenance of the proper potassium:sodium ratio in the endolymph is important for sensory transduction.

The cells thought to be responsible for the formation of vestibular endolymph are the dark cells.[25] Carbonic anhydrase, an enzyme that acts to catalyze the hydration of carbon dioxide and the dehydration of carbonic acid, has been localized in the dark cells.[26,27] The regulation of endolymph potassium concentration has been proposed as one function of inner ear carbonic anhydrase. Erulkar and Maren[28] demonstrated a marked decrease in the potassium concentration of endolymph after long-term treatment with acetazolamide. There was no significant change in the potassium concentration of the perilymph, which indicated that the change in the endolymph was not caused by a change in plasma potassium concentration. As mentioned above, alteration of the potassium:sodium ratio in the endolymph could have an effect on the polarization or current through the sensory hair cells and the potential for mechanical deformation of these cells. Both the standing current through the hair cells and the mechanical deformation of the cell membrane are involved in the process of transduction of motion into nerve impulses.[29] We believe that in our patients acetazolamide acted to decrease hair cell excitability, thereby decreasing vestibular input.

After thorough neurologic and neuro-ophthalmic examination has excluded other forms of episodic vertigo, we advocate a trial of acetazolamide in patients who appear to have episodic vertigo secondary to an abnormal oculovestibular response. Items on the shelves at the grocery store, seen peripherally while walking down the aisle, were a common stimulus among our patients. Six of our seven patients showed dramatic improvement in their symptoms as a result of treatment with acetazolamide. An appropriate initial dose would be 125 mg daily, because this seems to minimize the side effects. The dosage can then be increased, with most patients achieving resolution of symptoms while taking 250 to 500 mg daily. Regardless of the initial dosage, improvement is gradual, often requiring a month before significant improvement is noted. Although the mechanism of action of acetazolamide in the treatment of this form of episodic vertigo is unknown, we believe it to be the result of an altered potassium:sodium ratio in the endolymph. Further studies involving a greater number of patients with this affliction are needed to evaluate the possibility of placebo effect and further delineate the role of acetazolamide in the treatment of abnormal oculovestibular response.

References

1. Meyerhoff, W. L.: Abnormal oculovestibular response. Otolaryngol. Head Neck Surg. 99:24, 1988.
2. Donat, J. R., and Auger, R.: Familial periodic ataxia. Arch. Neurol. 36:568, 1979.
3. Fraunfelder, F. T., Meyer, S. M., Bagby, G. C., Jr., and Dreis, M. W.: Hematologic reactions to carbonic anhydrase inhibitors. Am. J. Ophthalmol. 100:79, 1985.
4. Kass, M. A.: Topical carbonic anhydrase inhibitors. Am. J. Ophthalmol. 107:280, 1989.
5. Paparella, M. M.: The cause (multifactoral inheritance) and pathogenesis (endolymphatic malabsorption) of Ménière's disease and its symptoms (mechanical and chemical). Acta Otolaryngol. 99:445, 1985.
6. Weiner, I. M., and Mudge, G. H.: Diuretics and other agents employed in the mobilization of edema fluid. In Gilman, A. G., Goodman, L. S., Rall, T. W., and Murad, F. (eds.): The Pharmacological Basis of Therapeutics, ed. 7. New York, Macmillan Publishing, 1985, pp. 887–907.
7. Becker, B., and Middleton, W. H.: Long term acetazolamide (Diamox) administration in therapy of glaucomas. Arch. Ophthalmol. 54:187, 1955.
8. Merlis, S.: Diamox. A carbonic anhydrase inhibitor. Neurology 4:863, 1954.
9. Huttenlocher, P. R.: Treatment of hydrocephalus with acetazolamide. J. Pediatr. 66:1023, 1965.
10. McArdle, B.: Adynamia episodica hereditaria and its treatment. Brain 85:121, 1962.
11. Resnick, J. S., Engel, W. K., Griggs, R. C., and Stam, A. C.: Acetazolamide prophylaxis in hypokalemic periodic paralysis. N. Engl. J. Med. 278:582, 1968.
12. Poskanzer, D. C., and Kerr, D. N. S.: A third type of periodic paralysis, with normokalemia and favorable response to sodium chloride. Am. J. Med. 31:328, 1961.

13. Griggs, R. C., Moxley, R. T., III, Riggs, J. E., and Engel, W. K.: Effects of acetazolamide on myotonia. Ann. Neurol. 3:531, 1978.

14. Evans, O. B., Kilroy, A. W., and Fenichel, G. M.: Acetazolamide in the treatment of pyruvate dysmetabolism syndromes. Arch. Neurol. 35:302, 1978.

15. Griggs, R. C., Moxley, R. T., III, LaFrance, R. A., and McQuillen, J.: Hereditary paroxysmal ataxia. Response to acetazolamide. Neurology 28:1259, 1978.

16. Sterkers, O., Ferrary, E., Saumon, G., and Amiel, C.: Na and nonelectrolyte entry into inner ear fluids of the rat. Am. J. Physiol. 253:F50, 1987.

17. Konishi, T., Hamrick, P. E., and Walsh, P. J.: Ion transport in guinea pig cochlea. I. Potassium and sodium transport. Acta Otolaryngol. 86:22, 1978.

18. Konishi, T., and Hamrick, P. E.: Ion transport in the cochlea of guinea pig. II. Chloride transport. Acta Otolaryngol. 86:176, 1978.

19. Sterkers, O., Saumon, G., Tran Ba Huy, P., and Amiel, C.: K, Cl, and H_2O entry in endolymph, perilymph, and cerebrospinal fluid of the rat. Am. J. Physiol. 243:F173, 1982.

20. Smith, C. A., Lowry, O. H., and Wu, M. L.: The electrolytes of the labyrinthine fluids. Laryngoscope 64:141, 1954.

21. Makimoto, K., Takeda, T., and Silverstein, H.: Chemical composition in various compartments of inner ear fluids. Arch. Otorhinolaryngol. 220:259, 1978.

22. Marcus, D. C.: Transepithelial electrical potential of nonsensory region of gerbil utricle in vitro. Am. J. Physiol. 251:C662, 1986.

23. Marcus, N. Y., and Marcus, D. C.: Potassium secretion by nonsensory region of gerbil utricle in vitro. Am. J. Physiol. 253:F613, 1987.

24. Tasaki, I.: Afferent impulses in auditory nerve fibers and the mechanism of impulse initiation in the cochlea. In Rasmussen, G. L., and Windle, W. F. (eds.): Neural Mechanisms of the Auditory and Vestibular System. Springfield, Charles C Thomas, 1961, pp. 40–47.

25. Kimura, R. S.: Distribution, structure, and function of dark cells in the vestibular labyrinth. Ann. Otol. Rhinol. Laryngol. 78:542, 1969.

26. Hsu, C. J., and Nomura, Y.: Carbonic anhydrase activity in the inner ear. Acta Otolaryngol. 418:1, 1985.

27. Lim, D. J., Karabinas, C., and Trune, D. R.: Histochemical localization of carbonic anhydrase in the inner ear. Am. J. Otolaryngol. 4:33, 1983.

28. Erulkar, S. D., and Maren, T. H.: Carbonic anhydrase and the inner ear. Nature 189:459, 1961.

29. Flock, A.: Sensory transduction in hair cells. In Loewenstein, W. R. (ed.): Handbook of Sensory Physiology, vol. 1. New York, Springer-Verlag, 1971, pp. 396–441.

OPHTHALMIC MINIATURE

Qwilleran winced and clenched his teeth and his eyes, only to feel the cat's whiskers tickling his eyelids. He jumped to a sitting position, and Koko bounded from the bed and from the room, mission accomplished.

When Qwilleran shuffled out of the bedroom, wearing his red plaid bathrobe and looking aimlessly for his pipe, he surveyed the living room with heavy-lidded eyes.

Lilian Jackson Braun, *The Cat Who Ate Danish Modern*
New York, G P. Putnam's Sons, 1967, p. 101

Reproducibility of Topographic Measurements of the Normal and Glaucomatous Optic Nerve Head With the Laser Tomographic Scanner

Andreas W. Dreher, Ph.D., Patrick C. Tso, B.A., and Robert N. Weinreb, M.D.

We acquired five independent topographic images of the optic nerve head of eight normal eyes and eight eyes with primary open-angle glaucoma with a laser tomographic scanner. Each image had a field of view of 15 × 15 degrees with a resolution of 256 × 256 pixels. The pixel size was approximately 15 × 15 μm. The value of a pixel of a topographic image represented the height at this position. The mean height and the standard deviation over the five topographic images were calculated for each of the 65,536 pixel positions. The standard deviation of a single height measurement in normal eyes was 38.7 μm (range, 23.4 to 62.2 μm) for areas in the peripapillary retina and 42.6 μm (range, 24.4 to 53.7 μm) for measurements within the optic nerve head area. In glaucomatous eyes, the standard deviation was 41.2 μm (range, 23.2 to 59.6 μm) in the peripapillary retina and 49.4 μm (range, 28.1 to 72.8 μm) within the optic nerve head. There was no significant difference between the standard deviation of a single height measurement in normal and glaucomatous eyes (P = .34 within the optic nerve head area; P = .57 on peripapillary retina). No correlation was found between standard deviation of the measurements and pupil size or age of the subject.

Evaluation of optic nerve head topography is important for diagnosing and managing glaucoma. Progressive optic nerve head cupping, a widening and deepening of the surface of the optic nerve head caused by either loss of neuroglial tissue or pressure-related compression with bowing of the lamina cribrosa, can precede measurable visual field defects.[1] In some cases, as many as half of the retinal ganglion cells can be lost before visual field defects can be detected.[2] Clinical methods for recording optic nerve head appearance include drawings and stereoscopic color photographs, which are qualitative and often inconsistent.[3,4] Several instruments have provided reproducible and accurate data of the optic nerve head by acquiring and analyzing digitized fundus images obtained with conventional optics.[5-7] High quality images, however, can be achieved only with large pupils and clear media, conditions often not encountered in older patients with primary open-angle glaucoma.

Another instrument has been developed for use in evaluation of glaucoma.[8-13] The laser tomographic scanner (LTS, Heidelberg Instruments, Inc., Heidelberg, Germany) uses a helium-neon laser beam to scan across the optic nerve head in three dimensions. It uses confocal detection, so that only the light reflected from a small region around the focal plane of its special optics is detected. This results in enhanced depth resolution over conventional imaging techniques. The measured values of the confocally detected light are used to produce a topographic map of the optic nerve head, which shows the height of each pixel of the image as compared with a reference plane. From these single height measurements, variables such as cup volume, cup depth, or retinal contour can be calculated.

The laser tomographic scanner provides contact-free imaging and measurement of the ocular fundus. It has several advantages over available clinical instruments.[8] Images often can be obtained in eyes with undilated pupils and

Accepted for publication Oct. 25, 1990.

From the Department of Ophthalmology, University of California, San Diego, California. This study was supported in part by Public Health grant EY05990 (Dr. Weinreb).

Reprint requests to Robert N. Weinreb, M.D., Department of Ophthalmology, University of California, San Diego, T-014, La Jolla, CA 92093.

cataracts. The instrument uses low light intensity, and a real-time image can be obtained for immediate evaluation.

In contrast to studies that examined the reproducibility of optic nerve head variables such as cup volume or cup/disk ratio,[6,7,12-14] we evaluated the reproducibility of the more basic measurement of height at a single location in the normal and glaucomatous optic nerve head with the laser tomographic scanner. The reproducibility of height measurements directly influences the variability of factors derived from these measurements.

Subjects and Methods

After informed consent, eight normal subjects and eight phakic patients with primary open-angle glaucoma were enrolled in this study. The study was approved by the Human Subjects Committee at the University of California, San Diego. The eyes with primary open-angle glaucoma had characteristic glaucomatous visual field loss and intraocular pressure exceeding 24 mm Hg on at least two separate examinations. In the group of normal subjects, there were four men and four women, with a mean age of 30 years (range, 22 to 50 years; Table 1). In the glaucoma group, there were three men and five women, with a mean age of 62 years (range, 34 to 74 years; Table 2). For each individual, one eye was selected randomly for study. The cup/disk ratio was estimated (Tables 1 and 2) by one of us (R.N.W.), who was masked to the results of the optic nerve head images.

TABLE 1
STANDARD DEVIATION OF TOPOGRAPHIC MEASUREMENTS IN NORMAL EYES*

CASE NO., AGE (YRS)	EYE IMAGED	PUPIL SIZE (MM)	REFRACTIVE ERROR (DIOPTERS)	CUP/ DISK RATIO	STANDARD DEVIATION (μM) OPTIC NERVE HEAD	STANDARD DEVIATION (μM) PERIPAPILLARY RETINA
1, 29	L.E.	2.5	−3.25	0.1	43.0	35.8
2, 25	R.E.	3.0	0	0.1	53.7	46.8
3, 31	R.E.	3.5	−4.0	0.5	42.9	34.4
4, 50	R.E.	2.5	+1.5	0.1	50.7	62.2
5, 32	R.E.	3.5	0	0.2	24.4	23.4
6, 27	L.E.	2.5	0	0.5	41.1	37.7
7, 22	L.E.	3.0	0	0.2	41.3	34.4
8, 27	L.E.	3.0	−2.5	0.3	43.9	34.7

*The pooled standard deviations were 42.6 μm for the optic nerve head and 38.7 μm for the peripapillary retina; the median standard deviations were 42.9 μm for the optic nerve head and 35.3 μm for the peripapillary retina.

TABLE 2
STANDARD DEVIATION OF TOPOGRAPHIC MEASUREMENTS IN GLAUCOMATOUS EYES*

CASE NO., AGE (YRS)	EYE IMAGED	PUPIL SIZE (MM)	REFRACTIVE ERROR (DIOPTERS)	CUP/ DISK RATIO	STANDARD DEVIATION (μM) OPTIC NERVE HEAD	STANDARD DEVIATION (μM) PERIPAPILLARY RETINA
9, 72	R.E.	7.5	−0.25	0.8	36.4	29.7
10, 65	L.E.	6.0	0	0.5	72.8	59.6
11, 71	R.E.	7.5	0	0.5	49.6	50.1
12, 44	L.E.	7.5	0	0.9	67.8	59.3
13, 34	R.E.	7.0	−2.75	0.4	33.4	26.9
14, 74	R.E.	8.0	−0.5	0.9	42.1	32.4
15, 73	L.E.	7.0	0	0.3	65.1	48.4
16, 63	L.E.	9.0	−1.5	0.8	28.1	32.2

*The pooled standard deviations were 49.4 μm for the optic nerve head and 41.2 μm for the peripapillary retina; the median standard deviations were 45.9 μm for the optic nerve head and 40.4 μm for the peripapillary retina.

A total of five independent sets of images of the optic nerve head were obtained for each individual on two separate days. Pupil diameters in the glaucomatous eyes were less than 2.0 mm as the result of miotic treatment. In these eyes, the miotic drug was discontinued 24 hours before examination, and the pupil was dilated with tropicamide 1.0% and phenylephrine hydrochloride 2.5% ophthalmic solutions. The pupils of normal eyes were not dilated. Pupil size was recorded slightly before image acquisition.

Detailed technical information describing the laser tomographic scanner has been described previously.[8-11] In brief, the real-time imaging system of the laser tomographic scanner uses a helium-neon laser beam that is scanned across the retina in x and y directions. By using confocal detection, only light reflected from the section of the retina lying at the focal plane of the scanning laser beam is detected. By changing the focal plane of the scanning laser beam, different section images can be recorded.

A fixation target light implemented in the laser tomographic scanner was used to position the eye for imaging. The operator adjusted the

laser intensity and the detector sensitivity. Then, the scan range along the optical axis was chosen by the operator. Imaging was initiated immediately anterior to the blood vessels as they emerged from the optic cup and was completed at a level posterior to the lamina cribrosa. A series of 32 equally spaced section images parallel to the retinal plane was obtained within this scan range. Each image in the series had a resolution of 256 × 256 pixels and covered a field of view of 15 × 15 degrees. The pixel size therefore was approximately 15 × 15 μm. A scan range between 1.0 and 2.5 mm was used.

The time to adjust the settings of the laser tomographic scanner to start image acquisition was between two and five minutes after the patient was positioned at the instrument. The actual acquisition time of a series of 32 section images was approximately four seconds. The images were recorded on an optical storage disk.

From these 32 section images, a software algorithm calculated the height at each of the 256 × 256 pixel positions to produce a topographic map (Fig. 1) of the area being examined.[8] The time for this procedure, which also included an algorithm to correct for any ocular movements during image acquisition, was approximately 90 seconds. To correct for any magnification errors, Zinser and associates[11] entered the refractive error and the corneal radius of curvature of the eye being examined. In our study, the refractive error of each eye and a value of 7.7 mm for the radius of curvature were used.

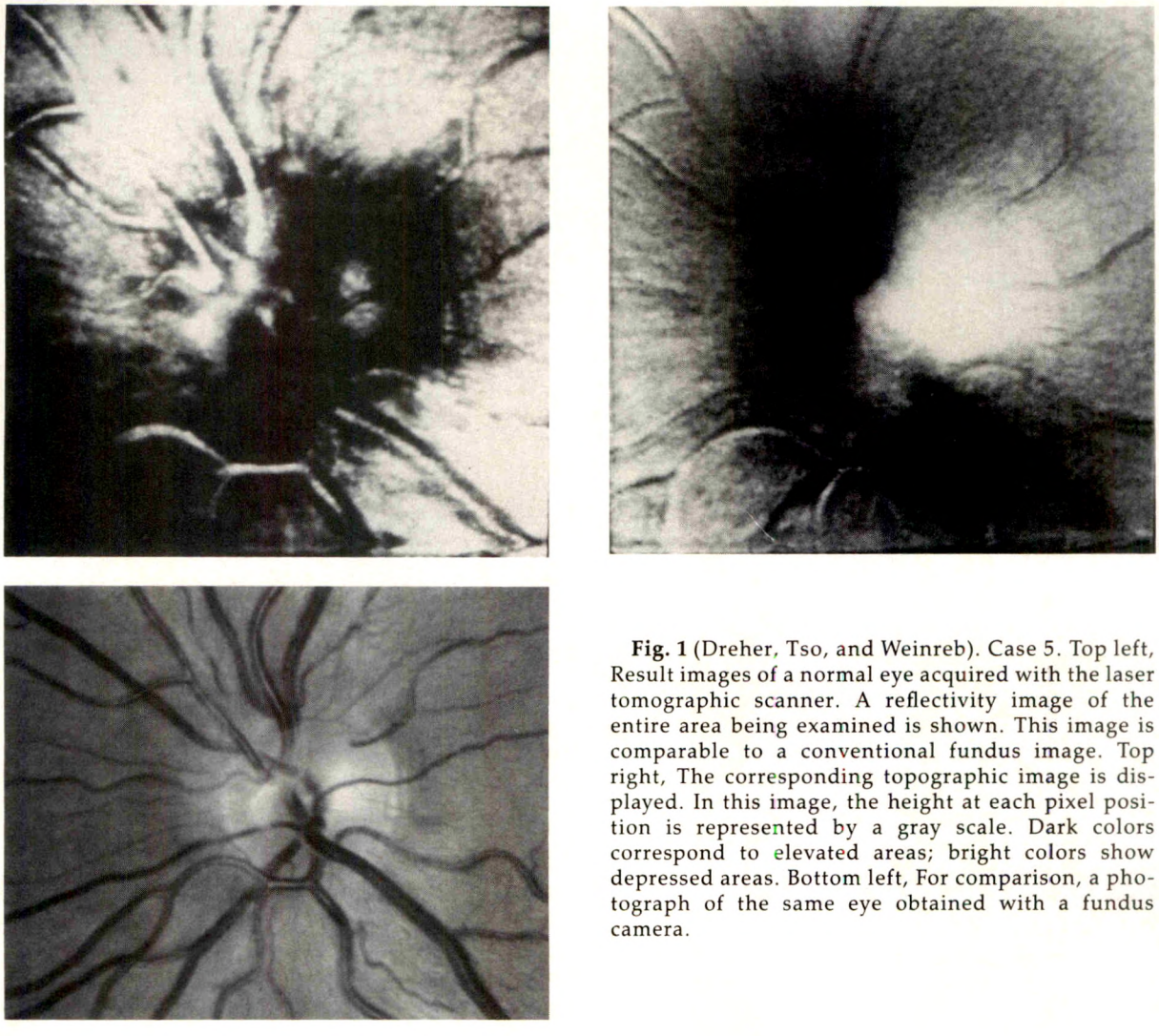


Fig. 1 (Dreher, Tso, and Weinreb). Case 5. Top left, Result images of a normal eye acquired with the laser tomographic scanner. A reflectivity image of the entire area being examined is shown. This image is comparable to a conventional fundus image. Top right, The corresponding topographic image is displayed. In this image, the height at each pixel position is represented by a gray scale. Dark colors correspond to elevated areas; bright colors show depressed areas. Bottom left, For comparison, a photograph of the same eye obtained with a fundus camera.

After calculating the five independent topographic images for each eye, one of the five height images was arbitrarily selected as the reference image for that eye. The remaining four topographic images were aligned in the x and y directions with the reference image. After shifting the images against each other, only the central part of the image that was common to all the five shifted images was used. Typically, the image size was reduced by up to 20% in each direction because of the shifting process. Next, these four shifted images were corrected for tilt and displacement relative to the reference image.

To define the retinal plane of the chosen reference height image, three points on the peripapillary retina were selected by the operator. These points were selected so as not to coincide with a blood vessel. Also, they were selected to be widely spread points to obtain a broad plane, thus minimizing errors from tilt. At each selected point, the average height value over an area of 10 × 10 pixels was calculated. The resulting three averaged height values were used to determine the reference plane. The same x and y coordinates of the three points also were used for the other four images in the same eye to define the retinal planes of those images. Since the images had been aligned previously in the x and y directions with the reference image, the three points selected were identical in all five images. The resulting five retinal planes then were corrected for tilt or offset among them. This resulted in one common reference plane for the five topographic images of each eye.

The height values at the same pixel location in the five corrected topographic images were used to calculate the mean and the variance at each pixel location. For each eye, the resulting values were displayed in one image representing the mean height (Fig. 2) and one image representing the standard deviation (square root of sample variance; Fig. 3) at each pixel position.

The operator then selected three points on the margin of the optic nerve head to approximate the rim of the optic nerve head by a circle. A computer algorithm calculated the average of the variances of the height measurements within and outside this defined area. Because of differences in magnification and changes in image size caused by the alignment procedure, the number of measurements in the optic nerve head was between 3,672 and 11,340 pixels, and the number of measurements at the peripapillary retina was between 27,864 and 35,532 pixels. The square roots of the average variances were the average standard deviations of single height measurements within or outside the optic nerve head.

In both the normal and glaucoma groups, the

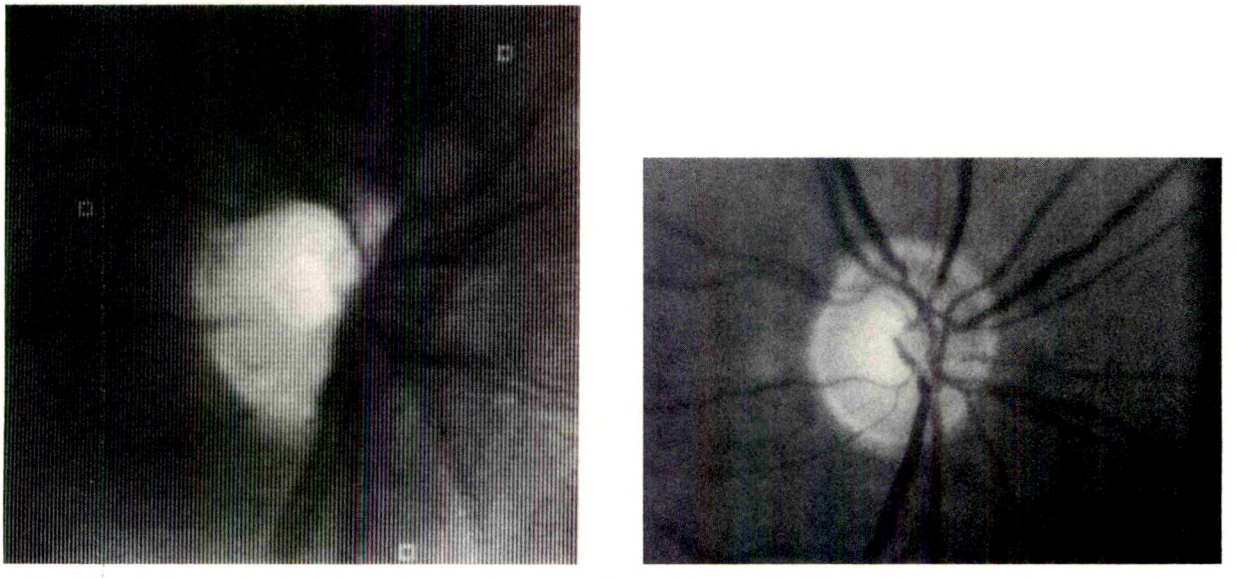


Fig. 2 (Dreher, Tso, and Weinreb). Case 11. Left, Image of a glaucomatous eye representing the mean height of each pixel over the set of five independent topographic images. The small squares indicate the locations of the three reference points for calculating the retinal plane for this image. Right, For comparison, a photograph of the same eye obtained with a fundus camera.

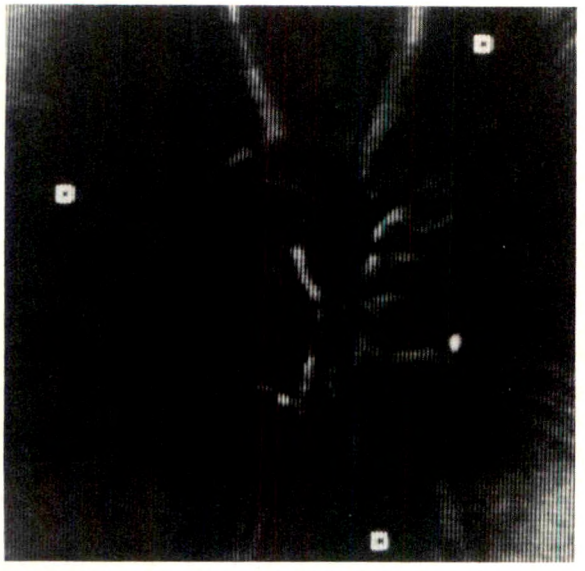


Fig. 3 (Dreher, Tso, and Weinreb). Case 11. Image representing the standard deviation of the height value at each pixel position. Light areas represent large standard deviations; dark colors represent small standard deviations. In this image, the range of standard deviations is from 11 μm (dark areas) to 114 μm (light areas). The small squares indicate the locations of the three reference points for calculating the reference plane for this image.

mean of the average standard deviations was calculated, and this was defined as the pooled standard deviation for the eight eyes in each group (Tables 1 and 2). An unpaired Student's *t*-test was used to compare the optic nerve head variabilities of the normal and glaucomatous eyes and the variabilities of the two groups in the peripapillary region. A P value of less than .05 was considered significant.

Results

The variability of a single height measurement within the optic nerve head of each eye was calculated using the five independent height images obtained for each eye. The pooled standard deviation of an optic nerve head height measurement from the normal eyes was 42.6 μm (range, 24.4 to 53.7 μm; Table 1). In the glaucomatous eyes, the pooled standard deviation of the optic nerve head height measurements was 49.4 μm (range, 28.1 to 72.8 μm; Table 2).

The pooled standard deviation of a single height measurement in the peripapillary retina of normal eyes was 38.7 μm (range, 23.4 to 62.2 μm; Table 1), and in the glaucomatous eyes was 41.2 μm (range, 23.2 to 59.6 μm; Table 2).

There were no statistical differences between the variability of the optic nerve head height measurements of the normal and glaucoma groups (P = .34) and between the variability of the peripapillary retinal height measurements of the two groups (P = .57). Also, the number of measurements (pixels) in the optic nerve head and peripapillary retina was not related to the variability.

The pooled variability from the height measurements outside the optic nerve head of both groups was lower than their corresponding values from the optic nerve head area. The differences, however, were not statistically significant (P = .45 for normal eyes; P = .38 for glaucomatous eyes).

The variability of the height measurements in relation to the age of the subjects is shown in Figures 4 and 5. The variability of the height measurements in relation to the pupil size is shown in Figure 6. A comparison of the frequency distributions of the standard deviations for age and pupil size showed no difference for either normal or glaucomatous eyes. Furthermore, the variability of the height measurement did not correlate with the amount of optic nerve head cupping, estimated by cup/disk ratio (Fig. 7).

Discussion

The difficulty of using coefficient of variation as a measure of variability when the variability of a measurement is not proportional to the mean was discussed by Shields and associates.[6] For our study, we evaluated reproducibility of topographic measurement of the optic nerve head with the laser tomographic scanner by determining the variability of individual pixels within the images. Our data show that the standard deviation of a single height measurement with the laser tomographic scanner is better than 50 μm for both normal and glaucomatous eyes. There was no statistical difference in variability of height measurements between the two groups. The pooled variability and the range of the variability values were similar for both groups tested. These measurements were independent of pupil size and cup/disk ratio.

The pooled variability of measurements at

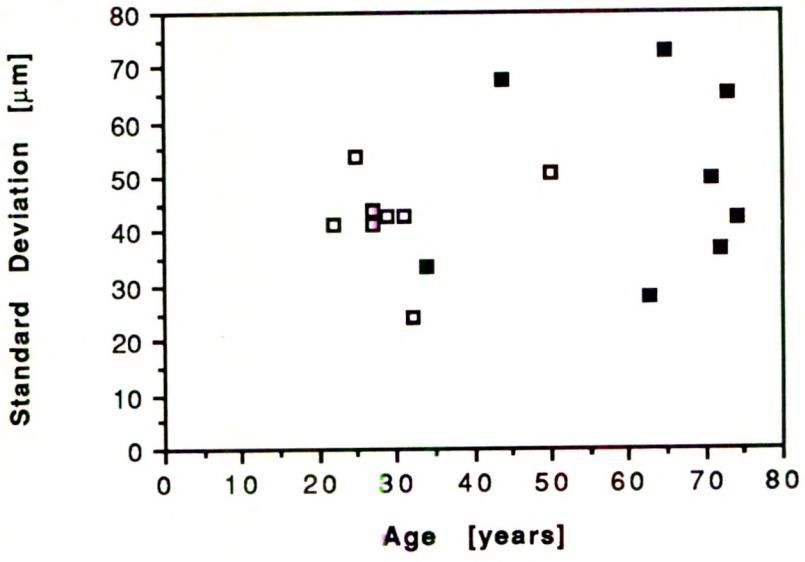


Fig. 4 (Dreher, Tso, and Weinreb). Variability of height measurements of the optic nerve head area of normal and glaucomatous eyes plotted against age of subject (normal eyes, open square; glaucomatous eyes, closed square).

the peripapillary retina of both groups was slightly lower than their corresponding values from the optic nerve head area. This may be related to the relative smoothness of the peripapillary retina compared to the optic nerve head area. Within the optic nerve head area, height values change frequently and abruptly because of the presence of many edges and blood vessels. This introduces a large gradient of topographic height values in these areas. In areas with large height gradients even a small misalignment of the five independent height images resulted in a larger standard deviation and, therefore, a reproducibility worse than that achieved in smooth areas. This is demonstrated in Figure 3, in which the standard deviation over the five height images of one optic nerve head is shown.

Several possibilities need to be considered to improve the variability of height measurements of the laser tomographic scanner. First, areas around blood vessels within the optic nerve head should be excluded for determining the variability of height measurements. In these areas, physiologic changes in the dimension and location of blood vessels during systole/diastole might be interpreted as a large variability in height. Second, consideration should be given to the definition of the retinal reference plane since it greatly influences variability.

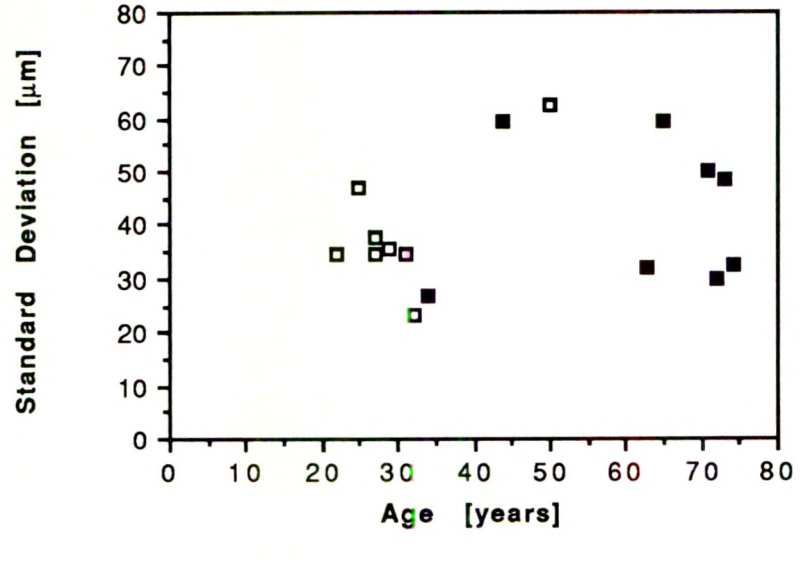


Fig. 5 (Dreher, Tso, and Weinreb). Variability of height measurements of the peripapillary retina of normal and glaucomatous eyes plotted against age of subject (normal eyes, open square; glaucomatous eyes, closed square).

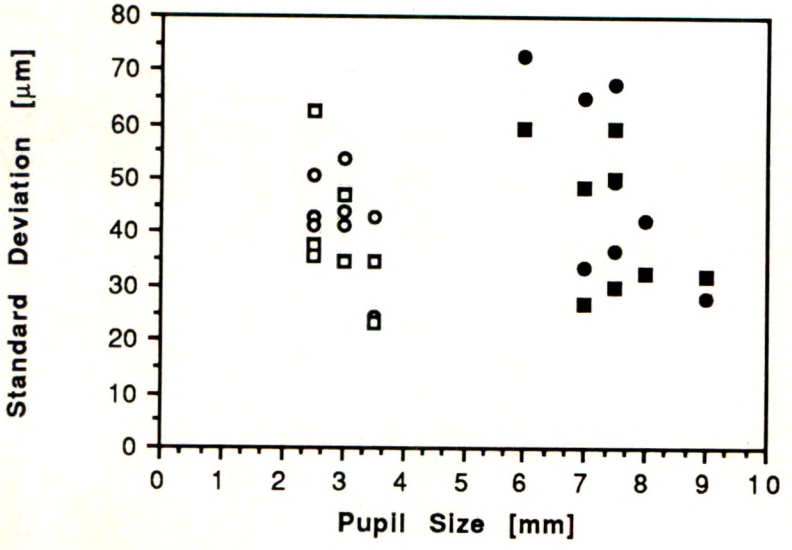


Fig. 6 (Dreher, Tso, and Weinreb). Variability of height measurements of the optic nerve head and peripapillary retina plotted against pupil size (normal optic nerve head, open circle; normal peripapillary retina, open square; glaucomatous optic nerve head, closed circle; glaucomatous peripapillary retina, closed square).

Miller and Caprioli[15] demonstrated that by choosing the three reference points of the retinal plane from standardized areas on the peripapillary retina there was an improvement of the height measurement variability of the Rodenstock Analyzer. A similar technique could be used with the laser tomographic scanner. Third, by reducing the number of measuring areas (by averaging the height values of several pixels), the sensitivity to minimal misalignment of the five topographic images of each subject would be greatly reduced, and a significant improvement of the variability data could be expected.

Previous reports of optic nerve head topography have relied upon data obtained by instruments that averaged height over an area corresponding to several pixels. In contrast, the laser tomographic scanner examines each pixel individually. The standard deviations we found are a measure of the variability with which the height of an area as small as 15 × 15 μm can be determined with one single measurement. By using areas larger than this, the reproducibility of the height measurement of this area is improved at the cost of decreased lateral resolution. Dandona, Quigley, and Jampel[16] reported the spacing between measuring locations to be approximately 100 × 100 μm (150 to 250 locations within optic nerve) for the Humphrey Retinal Analyzer (Allergan Humphrey, San Leandro, California). The same measuring area

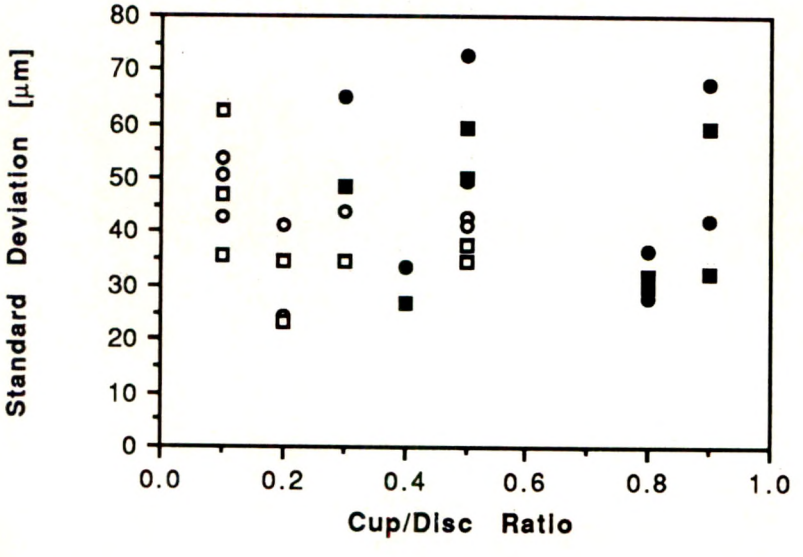


Fig. 7 (Dreher, Tso, and Weinreb). Variability of height measurements of the optic nerve head and peripapillary retina plotted against cup/disk ratio (normal optic nerve head, open circle; normal peripapillary retina, open square; glaucomatous optic nerve head, closed circle; glaucomatous peripapillary retina, closed square).

size of 100 × 100 μm is used with the Rodenstock Analyzer (G. Rodenstock Instrumente, Inc., Munich, Germany) as reported by Miller and associates.[17] According to Lim, Taylor, and Simmons,[18] the Imagenet Analyzer (Topcon Instrument Corporation of America, Paramus, New Jersey) calculates the height within the optic nerve head at approximately 600 individual locations from which a measuring area of approximately 50 × 50 μm can be estimated. The variability we found for height measurements with the laser tomographic scanner, therefore, cannot easily be compared with results found in previous reports. Furthermore, the variability as defined in most of these earlier reports depends on the number of repeated measurements. Dandona, Quigley, and Jampel[16] reported their findings as 95% confidence intervals that are based on ten repeated measurements per eye. They found pooled 95% confidence interval sizes (averaged over a group of ten subjects) from 165.6 μm for depth measurements in healthy eyes to 232.0 μm in glaucomatous eyes with a total range of 118.0 to 392.0 μm over all subjects. From these data, the corresponding range of standard deviations can be estimated to be from 26 to 85 μm. Lim, Taylor, and Simmons[18] reported the average 95% confidence interval for individual depth measurements in the optic nerve head as 280 μm. The number of repeated measurements was not reported and, therefore, one cannot estimate the standard deviation. Miller and associates[17] reported a standard deviation of 38 μm for fundus depth measurements at the peripapillary retina and a standard deviation of 61 μm for measurements within the optic nerve head.

Laser tomographic scanning is a rapid and convenient method for acquiring topographic information of the fundus. The variability of the height measurements is comparable to other methods with the advantage of a higher lateral resolution. The independence of the height measurement variability from pupil size, cup/disk ratio, and fundus location should make this technique clinically useful.

References

1. Quigley, H. A., Addicks, E. M., and Green, W. R.: Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. Arch. Ophthalmol. 100:135, 1982.

2. Quigley, H. A., Dunkelberger, G. R., and Green, W. R.: Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. Am. J. Ophthalmol. 107:453, 1989.

3. Shaffer, R. N., Ridgway, W. L., Brown, R., and Kramer, S. G.: The use of diagrams to record changes in glaucomatous disks. Am. J. Ophthalmol. 80:460, 1975.

4. Lichter, P. R.: Variability of expert observers in evaluating the optic disc. Trans. Am. Ophthalmol. Soc. 74:532, 1976.

5. Mikelberg, F. S., Airaksinen, P. J., Douglas, G. R., Schulzer, M., and Wijsman, K.: The correlation between optic disk topography measured by the video-ophthalmograph (Rodenstock analyzer) and clinical measurement. Am. J. Ophthalmol. 100:417, 1985.

6. Shields, M. B., Martone, J. F., Shelton, A. R., Ollie, A. R., and MacMillan, J.: Reproducibility of topographic measurements with the optic nerve head analyzer. Am. J. Ophthalmol. 104:581, 1987.

7. Weinreb, R. N., Nelson, M. R., Goldbaum, M. H., Brown, S. I., and Katz, B.: Digital image analysis of optic disk topography. In Blodi, F., Brancato, R., Cristini, G., d'Ermo, F., Esente, I., Musini, A., Philipson, B., Pintucci, F., Ponte, F., and Scuderi, G. (eds.): Acta XXV Concilium Ophthalmologicum. Proceedings of the 25th International Congress of Ophthalmology. Amsterdam, Kugler and Ghedini, 1987, p. 216.

8. Weinreb, R. N., Dreher, A. W., and Bille, J.: Quantitative assessment of the optic nerve head with the laser tomographic scanner. Int. J. Ophthalmol. 13:125, 1989.

9. Zinser, G., Wijnaendts-van-Resandt, R. W., Dreher, A. W., Weinreb, R. N., Harbarth, U., Schröder, H., and Burk, R. O. W.: Confocal laser tomographic scanning of the eye. Proc. SPIE 1161:337, 1989.

10. Dreher, A. W., Bille, J. F., and Weinreb, R. N.: Active-optical depth resolution improvement of the laser tomographic scanner. Appl. Optom. 28:804, 1989.

11. Zinser, G., Harbarth, U., Schröder, H., and Burk, R. O. W.: Formation and analysis of 3-dimensional data with the laser tomographic scanner. In Nasemann, J., and Burk, R. O. W. (eds.): Scanning Laser Ophthalmoscopy and Tomography. Munich, Quintessenz-Verlag, 1990, p. 115.

12. Kruse, F. E., Burk, R. O. W., Volcker, H. E., Zinser, G., and Harbarth, U.: Reproducibility of topographic measurements of the optic nerve head with laser tomographic scanning. Ophthalmology 96:1320, 1989.

13. Caprioli, J., Klingbeil, U., Sears, M., and Pope, B.: Reproducibility of optic disc measurements with computerized analysis of stereoscopic video images. Arch. Ophthalmol. 106:1035, 1986.

14. Varma, R., Steinmann, W. C., Spaeth, G. L.,

and Wilson, R. P.: Variability in digital analysis of optic disc topography. Graefes Arch. Clin. Exp. Ophthalmol. 226:435, 1988.

15. Miller, J. M., and Caprioli, J.: An optimal reference plane for measurement of peripapillary surface contour. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 566.

16. Dandona, L., Quigley, H. A., and Jampel, H. D.: Variability of depth measurements of the optic nerve head and peripapillary retina with computerized image analysis. Arch. Ophthalmol. 107:1786, 1989.

17. Miller, E. G., Miller, J. M., Hoffman, D., and Caprioli, J.: Spatial and temporal variation of fundus depth measurements. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1990, p. 459.

18. Lim, E. S., Taylor, S., and Simmons, S. T.: Variability of an optic disc change program. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 174.

OPHTHALMIC MINIATURE

It is not that I wanted to know a great deal, in order to acquire what is now called expertise, and which enables one to become an expert-tease to people who don't know as much as you do about the tiny corner you have made your own. I hoped for a bigger fish; I wanted nothing less than Wisdom. In a modern university if you ask for knowledge they will provide it in almost any form—though if you ask for out-of-fashion things they may say, like the people in shops, "Sorry, there's no call for it." But if you ask for Wisdom—God save us all! What a show of modesty, what disclaimers from the men and women from whose eyes intelligence shines forth like a lighthouse. Intelligence, yes, but of Wisdom not so much as the gleam of a single candle.

Robertson Davies, *The Rebel Angels*
New York, Penguin Books, 1982, p. 38

Mucogenic Secondary Open-Angle Glaucoma in Diffuse Epithelial Ingrowth Treated by Block-Excision

Michael Küchle, M.D., and Gottfried O. H. Naumann, M.D.

We treated a 40-year-old man with an acute, unilateral, open-angle glaucoma caused by a gelatinous translucent material in the anterior chamber. A clinical diagnosis of mucogenic secondary open-angle glaucoma caused by diffuse epithelial ingrowth after ocular trauma one year earlier was suspected, but a primary or secondary ciliary body or iris neoplasm could not be ruled out. A curative 9-mm block-excision was performed. Six years later, intraocular pressure was normal, and the visual function was unchanged. Light and electron microscopy disclosed an island of diffuse columnar epithelium with numerous goblet cells on the iris surface and copious mucinous material extending into the trabecular meshwork.

A VARIETY OF CELLS and matter can obstruct the ocular outflow passages, which produces an increase in intraocular pressure and leads to the various forms of secondary open-angle glaucoma.[1] A particular form of open-angle glaucoma caused by mucus occluding the trabecular meshwork has been described by Layden, Torczynski, and Font[2] from an iris biopsy and named mucogenic glaucoma.

We studied the clinical and histopathologic findings of a patient with posttraumatic, mucogenic, secondary open-angle glaucoma that was cured by block-excision.

Case Report

A 40-year-old man had a painful red left eye and rapidly deteriorating vision. The patient recalled having a foreign body injury, possibly a metal or vegetable matter foreign body, to his left eye one year earlier while grinding a piece of metal, but he did not consult an ophthalmologist at that time. When we first examined the patient in August 1983, best-corrected visual acuity was R.E.: 20/20 and L.E.: 20/700. Intraocular pressure by applanation tonometry was R.E.: 14 mm Hg and L.E.: 45 mm Hg. Slit-lamp examination, gonioscopy, and ophthalmoscopy of the right eye disclosed no abnormalities. The right optic disk appeared normal with a cup/disk ratio of 0.2. The red left eye showed a diffuse corneal edema particularly in the upper nasal quadrant without evidence of corneal scarring. Gonioscopically, the chamber angle was open and the anterior chamber contained a gelatinous translucent material and cells located on the iris between the pupillary area and the chamber angle in the nasal upper quadrant (Fig. 1). The lens was clear. On transillumination there was no gross extension of the lesion beyond the pars plicata of the ciliary body. The optic disk was atrophic with glaucomatous cupping and a cup/disk ratio of 0.9 to 1.0. The retina was attached and showed several small intraretinal hemorrhages in the midperiphery. On visual field testing using a Goldmann perimeter, there was a large absolute scotoma of the central area as well as the superotemporal, superonasal, and inferonasal quadrant with an island of vision in the inferotemporal quadrant extending from 20 to 70 degrees distance from the center.

The initial differential diagnoses included metastatic carcinoma, nonpigmented malignant melanoma, ciliary epithelial tumor (medulloepithelioma), and epithelial ingrowth. General examination did not disclose a primary tumor or any other abnormality. A presumed diagnosis of diffuse epithelial ingrowth with mucogenic glaucoma was made, and in August 1983, a 9-mm block-excision of the iris lesion, including pars plicata, sclera, and cornea of the nasal upper quadrant, was performed. The defect was covered with a tectonic corneal graft according to the previously described tech-

Accepted for publication Oct. 18, 1990.

From the Department of Ophthalmology, University of Erlangen-Nürnberg, Erlangen, Germany.

Reprint requests to Michael Küchle, M.D., Department of Ophthalmology, University Erlangen-Nürnberg, Schwabachanlage 6, D-8520 Erlangen, Germany.

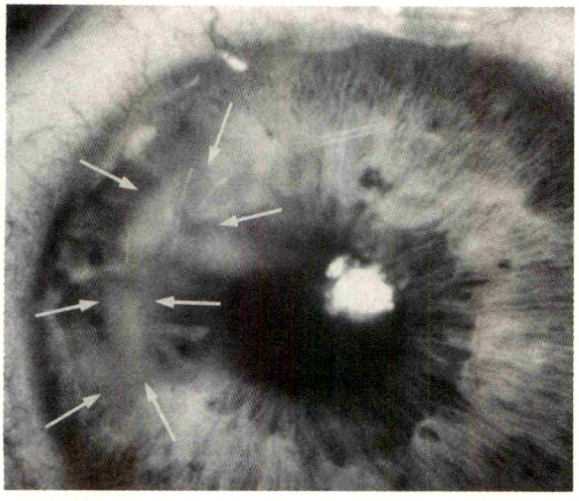


Fig. 1 (Küchle and Naumann). Preoperative appearance of right eye showing a hazy, gelatinous, translucent material (arrows) in the anterior chamber that makes the iris surface appear somewhat blurred.

nique.[3,4] The operative and postoperative course were unremarkable. Postoperatively, intraocular pressure of the left eye was regulated and has remained normal without antiglaucoma medication. Visual acuity and visual field remained unchanged as a result of the glaucomatous optic atrophy.

The patient was last examined in July 1989, almost six years after surgery, when he was comfortable and pain free. Visual acuity was R.E.: 20/20 and L.E.: 20/700. Intraocular pressure by applanation tonometry was R.E.: 17 mm Hg and L.E.: 14 mm Hg. The left eye showed a marked afferent pupillary defect. The corneal transplant was centrally clear and showed some scarring and vascularization near the corneoscleral limbus. There was an operative sector coloboma of the iris in the nasal superior quadrant. The anterior chamber was clear. The chamber angle was open. The lens was in place and showed some posterior subcapsular opacities but was clear otherwise. Examination of the optic disk and visual field testing of the left eye disclosed advanced glaucomatous damage that was unchanged from the preoperative findings in August 1983.

Results

The excised tissue of 9-mm diameter consisted of cornea, sclera, pars plicata of the ciliary body, iris, and a gray material in the anterior chamber, and the chamber angle (Fig. 2) and was sectioned in halves.

Histologically, the structures of the anterior chamber sinus were open. The iris surface was partially covered by multilayered nonkeratinizing stratified columnar epithelium that contained many goblet cells (Figs. 3 and 4). The chamber angle and trabecular meshwork were covered by a mucinous structure that showed positive staining for colloidal iron, periodic acid-Schiff, and mucicarmine and was resistant to hyaluronidase. Adjacent to the epithelial

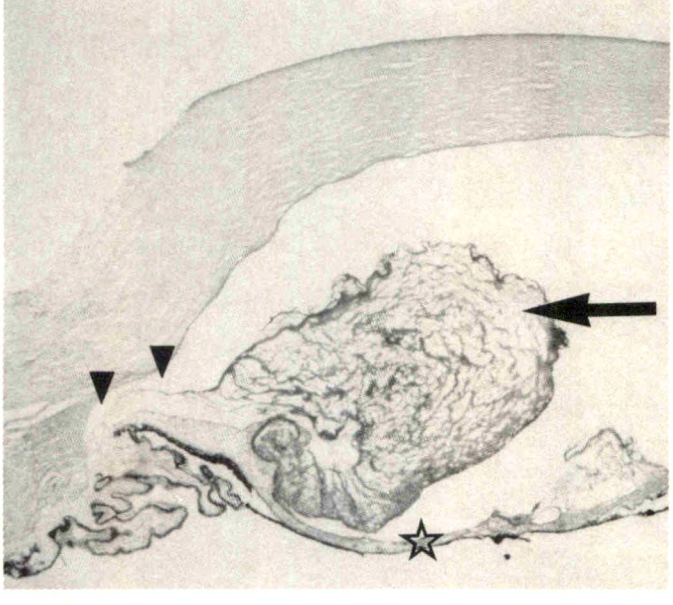


Fig. 2 (Küchle and Naumann). Photomicrograph of excised tissue. Mucinous material (arrows) is found on the iris surface (star) and in the anterior chamber extending into the chamber angle. The chamber angle itself is freely accessible (arrowheads) (periodic acid-Schiff, × 15).

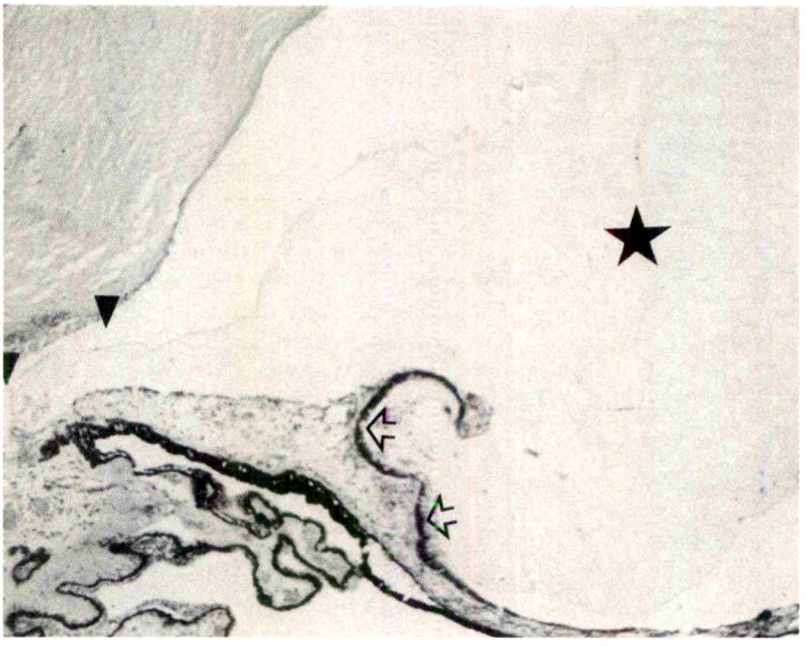


Fig. 3 (Küchle and Naumann). Photomicrograph showing columnar epithelium on iris surface (arrows) and gelatinous material (star) in the anterior chamber. The chamber angle is open (arrowheads) (hematoxylin and eosin, ×40).

island, a foreign body of approximately 500 μm was present. In serial sections, there was no evidence of epithelial lining of the trabecular surface, and no scar of a perforating injury could be demonstrated.

Transmission electron microscopy showed the iris covered by columnar epithelium with microvilli and numerous goblet cells secreting mucin (Figs. 5 and 6). There were mucin droplets between the trabecular meshwork (Fig. 7) and numerous amorphous inclusions within the endothelial lining of the trabecular meshwork. No viable epithelial cells were seen on or within the trabecular meshwork.

The final histologic diagnoses were the following: epithelial ingrowth on the iris with massive mucus production; secondary mucogenic open-angle glaucoma without epithelial lining of the trabecular meshwork; and intraocular foreign body on the iris surface.

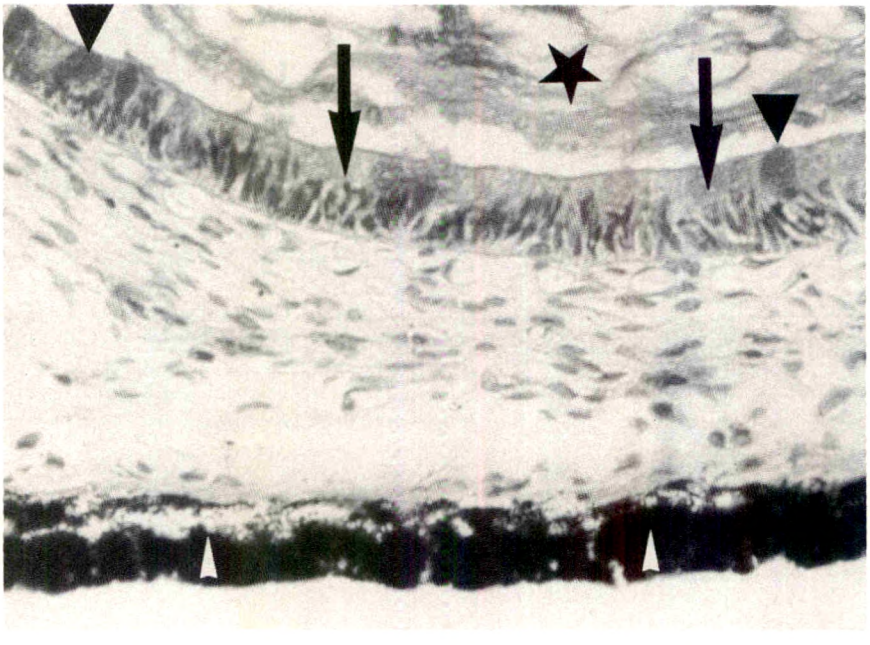


Fig. 4 (Küchle and Naumann). Photomicrograph of excised iris. Note multilayered nonkeratinizing stratified columnar epithelium (arrows) containing numerous goblet cells (black arrowheads) on iris surface and mucinous material (star) anterior to the iris. White arrowheads indicate iris pigment epithelium (periodic acid-Schiff, ×250).

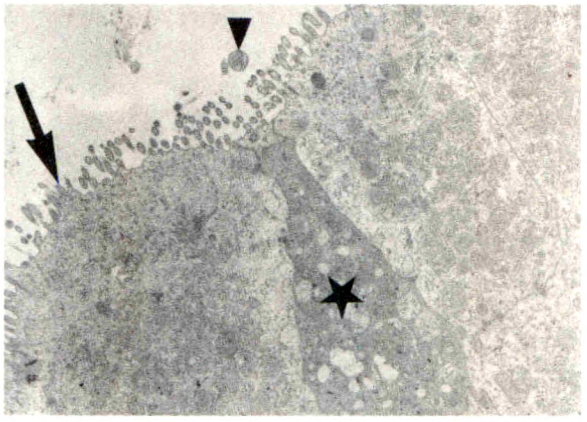


Fig. 5 (Küchle and Naumann). Columnar epithelium covering the iris surface. Note microvilli (arrow) and a goblet cell (star) secreting a mucin droplet (arrowhead) (× 3,400).

Discussion

Secondary mucogenic open-angle glaucoma seems to be a rare complication of trauma or surgery. In contrast to the patient described by Layden, Torczynski, and Font,[2] in our patient the traumatic origin of the lesion seems certain. The patient had a foreign body injury to his left eye one year before the first examination, and the histologic studies disclosed an intraocular foreign body on the excised iris, although no scar of a perforating wound could be demonstrated in serial sections.

Invasion of conjunctival epithelial cells is a serious complication of perforating injuries and of intraocular surgery.[5,6] The invading epithelium may either form an epithelial cyst in the anterior chamber or grow diffusely on the back of the cornea, the iris surface, the trabecular meshwork, the ciliary body, and the anterior vitreous face.[7-9] The diffuse form of epithelial ingrowth is frequently associated with secondary open-angle glaucoma caused by epithelial lining of the trabecular meshwork, with the glaucoma sometimes being masked by fistulization of the intraocular epithelium to the ocular surface. Diffuse epithelial ingrowth is difficult to treat because of frequent recurrence if the surgical excision of the invading epithelium is incomplete.[3,10,11]

In our patient, however, the secondary open-angle glaucoma was not caused by epithelial ingrowth on the trabecular meshwork, as proved histologically in serial sections by the absence of epithelial lining on the freely accessible trabecular meshwork. Similar to the previous patient with mucogenic glaucoma,[2] the glaucoma apparently originates from copious mucous material obstructing the ocular aqueous outflow pathways. By electron microscopy we were able to demonstrate numerous amorphous inclusions within the endothelial cells of the trabecular meshwork.

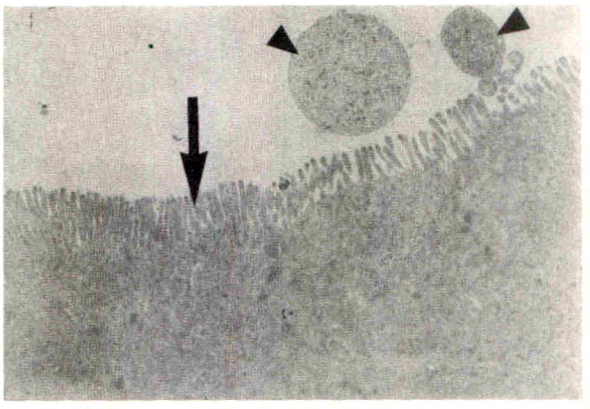


Fig. 6 (Küchle and Naumann). Columnar epithelium with microvilli (arrow) covering the iris surface. Note mucin droplets (arrowheads) (× 3,400).

The clinical differential diagnoses in our patient included diffuse epithelial ingrowth, nonpigmented malignant melanoma, medulloepithelioma of the ciliary body perforating the iris root, and metastatic carcinoma. The history of an ocular injury and the clinical findings made

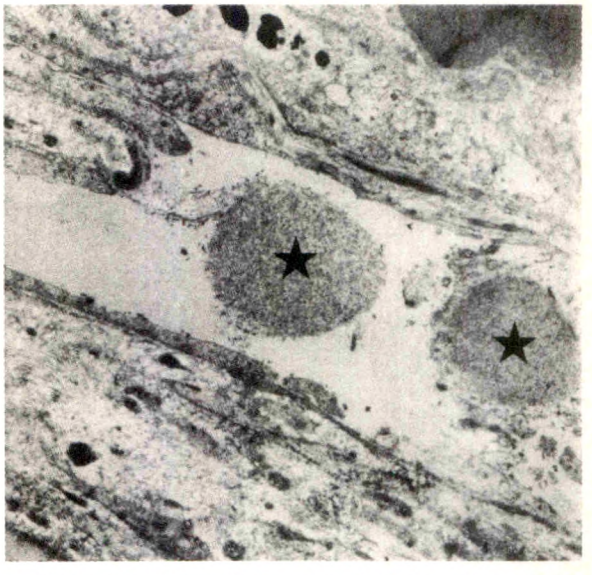


Fig. 7 (Küchle and Naumann). Trabecular meshwork with intercellular mucin droplets (star) (× 8,500).

the clinical diagnosis of diffuse epithelial ingrowth with secondary mucogenic glaucoma most likely. As it was impossible clinically to evaluate the extent of chamber angle and ciliary body involvement of epithelial ingrowth, a block-excision of the iris lesion including the chamber angle structures, pars plicata, and cornea was performed to make sure that all implanted epithelium was excised. By excision of the epithelial implantation, including the mucus-producing goblet cells, the source of the trabecular blockade was removed, and the glaucoma was cured. In reflecting on our case retrospectively and examining the histopathologic specimens, however, a local excision of the lesion only with the adjacent iris tissue might have been sufficient, but this possibility could not be foreseen preoperatively when care was taken to remove all implanted epithelial cells completely. During the follow-up of 71 months, intraocular pressure was normal and no recurrence of mucus-producing epithelium occurred in our patient. The visual acuity and visual field, however, could not be improved because of the preexisting glaucomatous optic atrophy.

In contrast to diffuse epithelial ingrowth, secondary mucogenic open-angle glaucoma seems to be rare. The factors causing mucogenic glaucoma or making an eye susceptible to it are not completely understood. Definitively, a substantial number of conjunctival epithelium-containing goblet cells must be implanted into the anterior chamber for mucogenic glaucoma to develop. The growth and mucus production of goblet cells might be influenced, and possibly enhanced, by local or humoral factors in the eye.[12]

In patients with subacute or acute open-angle glaucoma after an ocular injury, mucogenic glaucoma should be included in the differential diagnosis. Clinical findings of mucogenic glaucoma include an open chamber angle, a gelatinous mass on the iris, and a hazy, mucinous substance in the anterior chamber and the chamber angle. It is important that mucogenic glaucoma be diagnosed early before irreversible glaucomatous changes have occurred, because it can be cured by complete surgical excision of the mucus-producing tissue if less than 150 degrees of the circumference of the chamber angle are involved.

ACKNOWLEDGMENT

Peter Enke, M.D., provided the electron microscopic studies of this patient.

References

1. Naumann, G. O. H.: Glaucoma and ocular hypotony. Pathology of abnormal intraocular pressure. In Naumann, G. O. H., and Apple, D. J. (eds.): Pathology of the Eye, chap. 14. New York, Springer-Verlag, 1986, pp. 803–812.

2. Layden, W. E., Torczynski, E., and Font, R. L.: Mucogenic glaucoma and goblet cell cyst of the anterior chamber. Arch. Ophthalmol. 96:2259, 1978.

3. Naumann, G., and Völcker, H. E.: Blockexzision intraokularer Prozesse. II. Epitheleinwachsung in das vordere Augensegment. Klin. Monatsbl. Augenheilkd. 166:448, 1975.

4. Naumann, G. O. H.: Blockexzision bei zystischer und diffuser Epitheleinwachsung. In Heilmann, K., and Paton, D. (eds.): Atlas der ophthalmologischen Operationen, Band II. Stuttgart, Thieme, 1988, pp. 125–130.

5. von Domarus, D., and Naumann, G. O. H.: Accidental and surgical trauma and wound healing of the eye. In Naumann, G. O. H., and Apple, D. J. (eds.): Pathology of the Eye, chap. 5. New York, Springer-Verlag, 1986, pp. 193–196.

6. Stark, W., and Bruner, W. E.: Epithelial ingrowth and fibrous proliferation. In Ritch, R., and Shields, M. B. (eds.): The Secondary Glaucomas. St. Louis, C. V. Mosby, 1982, pp. 381–386.

7. Jensen, P., Minckler, D. S., and Chandler, J. W.: Epithelial ingrowth. Arch. Ophthalmol. 95:837, 1977.

8. Zavala, E. Y., and Binder, P. S.: The pathologic findings of epithelial ingrowth. Arch. Ophthalmol. 98:2007, 1980.

9. Smith, R. E., and Parrett, C.: Specular microscopy of epithelial downgrowth. Arch. Ophthalmol. 96:1222, 1978.

10. Maumenee, A. E., Paton, D., Morse, P. H., and Butner, R.: Review of 40 histologically proven cases of epithelial downgrowth following cataract extraction and suggested surgical management. Am. J. Ophthalmol. 69:598, 1970.

11. Stark, W. J., Michels, R. G., Maumenee, A. E., and Cupples, H.: Surgical management of epithelial ingrowth. Am. J. Ophthalmol. 85:772, 1978.

12. Cogan, D. G.: Experimental implants of conjunctiva into the anterior chamber. Am. J. Ophthalmol. 39:165, 1955.

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

EDITORIAL BOARD

Thomas M. Aaberg, *Atlanta*
Jules Baum, *Boston*
William M. Bourne, *Rochester*
Ronald M. Burde, *New York*
Fred Ederer, *Bethesda*
Frederick T. Fraunfelder, *Portland*
Michael A. Kass, *St. Louis*
Steven G. Kramer, *San Francisco*
Irving H. Leopold, *Irvine*
Robert Machemer, *Durham*
Nancy M. Newman, *San Francisco*
Don H. Nicholson, *Miami*
Edward W. D. Norton, *Miami*
Deborah Pavan-Langston, *Boston*
Allen M. Putterman, *Chicago*
Dennis Robertson, *Rochester*
Merlyn M. Rodrigues, *Baltimore*
Stephen J. Ryan, *Los Angeles*
Jerry A. Shields, *Philadelphia*
M. Bruce Shields, *Durham*
Ronald E. Smith, *Los Angeles*
Bruce E. Spivey, *San Francisco*
Bradley R. Straatsma, *Los Angeles*
H. Stanley Thompson, *Iowa City*
E. Michael Van Buskirk, *Portland*
Gunter K. von Noorden, *Houston*

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

Edward W. D. Norton, *President*
Bradley R. Straatsma, *Vice President*
Frank W. Newell, *Secretary and Treasurer*
Bruce E. Spivey
Thomas M. Aaberg
Michael A. Kass

PERSPECTIVES

Automated Perimetry in Glaucoma

Joseph Caprioli, M.D.

The realization that measurements of intraocular pressure have limited value to diagnose glaucoma has accentuated the importance of evaluating the structural and functional abnormalities caused by glaucoma. The contemporary care of patients with glaucoma requires careful, sequential recordings of the visual field and the appearance of the optic disk. Automated perimetry is a ready means to obtain standardized, quantitative measurements of the visual field, has prompted valuable clinical research, and has improved the care of patients with glaucoma.

Static threshold measurements are sensitive to shallow depressions of the visual field. This increases the detection rate of early glaucomatous defects compared to routine manual techniques.[1-5] Although static threshold measurements are not new to practitioners, the computerized format and the generation of a large amount of numeric data present new challenges. The increased sensitivity of the method has increased the "noise" of the measurements and demands careful attention to the many variables that may affect the measured threshold. Visual field measurements should never be interpreted in the absence of other clinical information. It is necessary to integrate intraocular pressure, appearance of the optic nerve, and other ocular, systemic, historical, and social factors when making decisions about diagnosis and therapy.

The mainstay of automated glaucoma testing has been the central 30-degree field programs. In patients with advanced visual loss, programs designed to test a small area of central field with high resolution are time-efficient since nonseeing areas are not tested and seeing areas are tested with high resolution. Measurements of the peripheral nasal field may detect early defects in glaucoma when none are present in the central 30 degrees, an event that occurs at the rate of 10% to 15%.[6,7] Computerized kinetic perimetry has recently been introduced and initial reports are encouraging, but its reliability and reproducibility have yet to be estab-

lished.[8,9] The most time-efficient way to test the peripheral field in glaucoma has yet to be determined.

The differential light sensitivity begins to decrease at an early age (20 years) and continues to decrease at a fairly constant rate throughout life.[10] The decline of sensitivity is location-dependent: the sensitivity of the peripheral field decreases more than that of the central field. The profile of visual sensitivity thus becomes steeper in the periphery with age. The variability of responses in normal individuals is greater in the periphery than in the center.[11] The difference between a measured value for the patient and a normal value must therefore be greater in the periphery than in the central field if the difference is to be considered significant. Variability may also increase with age, though this effect remains uncertain.[12,13]

Patient reliability is an important initial consideration when interpreting visual fields. This may be assessed by the rates of false-positive and false-negative answers; the operator's assessment of reliability; the fluctuation of repeated threshold measurements; the number of fixation losses; and the number of stimulus presentations required to complete a visual field examination. A simplified scheme to gauge patient reliability is presented in Table 1. The operator must adequately explain the testing procedure and encourage patient cooperation and alertness during the examination if reliable results are to be obtained.

Abnormalities of the visual field can be recognized in two ways: by point-by-point comparison with data from normal individuals of similar age, and by comparison with thresholds in adjacent areas of the visual field, in the opposite hemifield of the same eye, or in the visual field of the contralateral eye. Criteria for abnormality must remain pliable by other clinical considerations. Rigid criteria will lead to overdiagnosis of visual field defects in some and underdiagnosis in others. The criteria should depend on one's level of suspicion for glaucomatous optic nerve damage. If strict criteria are used, specificity for glaucomatous defects will be high but sensitivity will be low; if one uses liberal criteria, sensitivity will be high but specificity will be low. Examples of graded criteria are provided as a framework for interpretation (Table 2) but should not be used as an imperative set of rules. A repeat examination should be performed whenever possible to confirm the presence of a new or subtle defect, especially when the presence of such a defect may prompt a surgical decision.

TABLE 1
VISUAL FIELD RELIABILITY SCORE

CRITERIA	SCORE
1) Rate of false-negative catch trials	
(if < 8 trials, score = 0)	
≥ 10% and < 20%	1
≥ 20% and < 30%	2
≥ 30%	3
2) Rate of false-positive catch trials	
(if < 8 trials, score = 0)	
> 20% (≥ 8 trials)	1
3) Subjective grading of performance	
by perimetrist	
Good to excellent	0
Fair	1
Poor	2
Terrible	3
4) Short-term fluctuation	
> 4.0 dB	1
5) Fixation losses	
> 15% of trials	1
6) Total number of stimuli*	
> 550 (for standard 30-degree programs)	1
> 400 (for standard 24-degree programs)	1
The maximum total score is 10.	
Score = 0 — Reliable	
Score = 1–2 — Probably reliable	
Score = 3–5 — Results suspect	
Score > 5 — Interpret with great caution	

*Note that eyes with advanced abnormalities will require more stimuli to complete the examination than eyes with little or no defect.

The classic glaucomatous visual field defects are often preceded by widespread, shallow depressions throughout the visual field, though the concept of uniform diffuse depression in early glaucoma is debated.[14,15] Diffuse depression is not specific for glaucoma and is frequently caused by media opacity, inaccurate refraction, miosis, retinal disease, or poor test performance. Computer-assisted comparisons with normal data may help identify early glaucomatous defects. Probability maps that take regional variability into account are most helpful.[16,17] The visual field indices mean defect (or mean deviation), corrected loss variance (or corrected pattern standard deviation), and short-term fluctuation, originally introduced by Flammer and associates,[18] seem useful to evaluate sequential examinations[19] but may not be suited to detect the earliest glaucomatous defects.[20]

TABLE 2
EXAMPLES OF CRITERIA FOR ABNORMALITY
(CENTRAL 30 DEGREES)

Strict
≥ 4 adjacent points of ≥ 5 dB loss* each
≥ 3 adjacent points of ≥ 10 dB loss* each
Difference of ≥ 10 dB across nasal horizontal meridian at ≥ 3 adjacent points
Exclusions: physiologic blind spot; superior and inferior rows
Moderate
≥ 3 adjacent points of ≥ 5 dB loss* each
≥ 2 adjacent points of ≥ 10 dB loss* each
Difference of ≥ 10 dB across nasal horizontal meridian at ≥ 2 adjacent points
Exclusions: physiologic blind spot; superior and inferior rows
Liberal
≥ 2 adjacent points of ≥ 5 dB loss* each
≥ 1 adjacent point of ≥ 10 dB loss* each
Difference of ≥ 5 dB across nasal horizontal meridian at ≥ 2 adjacent points

*Loss is relative to normal values or to values of surrounding points. For probability maps that compare measured thresholds to normal values one may substitute $P < .05$ for 5 dB loss, and $P < .01$ for 10 dB loss.

Careful comparison of sequential visual fields often appropriately directs glaucoma treatment. Knowledge of the conditions under which valid comparisons can be made is essential. It is best to avoid changes in treatment, whenever possible, based on the comparison of only two visual fields. A series of examinations may show the true course of the disease when only two examinations would be misleading. There are no generally accepted criteria for progression of defects, but some guidelines can be offered. A new, confirmed defect that meets reasonable criteria for abnormality can be considered progression. In areas of a previous defect, a further decrease in the threshold of greater than or equal to 5 dB would be suggestive, whereas a decrease of greater than or equal to 10 dB can usually be considered a significant change.

A number of confounding variables make the interpretation of visual fields difficult, particularly for progression. The differentiation of long-term fluctuation (test-retest variation) from true progression of visual field loss remains one of the important challenges in modern perimetry. Long-term fluctuation in glaucomatous eyes increases with the depth of the defect and with distance from fixation.[21-23] The comparison of sequential visual fields is enhanced if these factors are considered. Computer-assisted analyses have been developed to evaluate sequential visual field examinations for evidence of progression beyond that which might be explained, at a given level of probability, by long-term fluctuation. The practitioner must be cautioned, however, that statistical significance should not be equated with clinical significance.

Changes in pupil area by a factor of four or more can significantly affect the visual field, and may be exaggerated in the presence of even minor media opacities. Pupil size should be measured and recorded at every visual field examination; when it is less than 3.0 mm, patients' pupils should be dilated before testing whenever possible. When this is not possible, examinations should be repeated at the same pupil size.

Cataract can have a profound effect on measured visual thresholds, especially in the presence of a small pupil. A subjective evaluation of the media is useful, but such evaluations are rarely sensitive enough to detect small changes that can significantly affect visual field measurements. Quantitative measurements of light scattering by the crystalline lens may be helpful.[24] In difficult situations in which changes in media clarity have occurred, it helps to correlate apparent deterioration of the visual field with change in optic nerve appearance. Stereophotographs of the optic disk are indispensable in this regard.

Refractive errors of only one diopter can cause a significant decrease of measured central visual thresholds.[25,26] Aphakic eyes are best tested after placement of contact lenses, since aphakic spectacle correction induces significant peripheral artifact.

The results of psychophysical tests generally improve as subjects gain experience. This learning effect is small in most patients who have previous experience with manual perimetry, but some patients still show a dramatic improvement on their second automated test compared to their first. The variability of test results decreases significantly with experience.[27] Whenever possible, the patient's second visual field test should be used as a baseline for subsequent comparisons.

The weight given to perimetric findings in decision making depends on the reliability of the patient, the visibility and appearance of the optic nerve, the level and trend of intraocular pressure, and ocular, systemic, historical, and

social factors. Computerized static threshold perimetry has increased the validity of routinely performed visual field examinations. It has made comparisons of multiple examinations more meaningful, but also more problematic. Automated perimetry has properly shifted the emphasis away from intraocular pressure measurements and toward the visual field in the diagnosis and treatment of glaucoma. Perimetric results, when they are reliable, should play prominently in the minds of practitioners when making diagnostic and therapeutic decisions.

Future work to enhance the value of automated perimetry will undoubtedly include the development of summary indices with improved sensitivity and specificity for early glaucomatous defects; better strategies to differentiate true progression from long-term fluctuation; and time-saving testing algorithms with acceptable detection rates for early defects. Automated perimetry has, perhaps, provided more questions than answers about the early functional abnormalities in glaucoma. The sensitivity of the technique has made us more aware of the "noise" inherent in psychophysical testing; improved techniques to separate the "signal" from the "noise" must be developed.

From the Department of Ophthalmology and Visual Science, Glaucoma Service, Yale University School of Medicine, New Haven, Connecticut.

Reprint requests to Joseph Caprioli, M.D., Department of Ophthalmology and Visual Science, Yale University School of Medicine, 330 Cedar St., New Haven, CT 06510-8061.

References

1. Heijl, A.: Automatic perimetry in glaucoma visual field screening. A clinical study. Graefes Arch. Clin. Exp. Ophthalmol. 200:21, 1976.

2. Fankhauser, F., Spahr, J., and Bebie, H.: Some aspects of the automation of perimetry. Surv. Ophthalmol. 22:131, 1977.

3. Li, S. G., Spaeth, G. L., Scimeca, H. A., Schatz, N. J., and Savino, P. J.: Clinical experiences with the use of an automated perimeter (Octopus) in the diagnosis and management of patients with glaucoma and neurologic diseases. Ophthalmology 86:1302, 1979.

4. Dyster-Aas, K., Heijl, A., and Lundquist, L.: Computerized visual field screening in the management of patients with ocular hypertension. Acta Ophthalmol. 58:918, 1980.

5. Hotchkiss, M. L., Robin, A. L., Quigley, H. A., and Pollack, I. P.: A comparison of peritest automated perimetry and Goldmann perimetry. Arch. Ophthalmol. 103:397, 1985.

6. Caprioli, J., and Spaeth, G. L.: Static threshold examination of the peripheral nasal visual field in glaucoma. Arch. Ophthalmol. 103:1150, 1985.

7. Seamone, C., LeBlanc, R., Rubillowicz, M., Mann, C., and Orr, A.: The value of indices in the central and peripheral visual fields for the detection of glaucoma. Am. J. Ophthalmol. 106:180, 1988.

8. Stewart, W. C., Shields, M. B., and Ollie, A. R.: Peripheral visual field testing by automated kinetic perimetry in glaucoma. Arch. Ophthalmol. 106:202, 1988.

9. Miller, K. N., Shields, M. B., and Ollie, A. R.: Automated kinetic perimetry with two peripheral isopters in glaucoma. Arch. Ophthalmol. 107:1316, 1989.

10. Haas, A., Flammer, J., and Schneider, U.: Influence of age on the visual fields of normal subjects. Am. J. Ophthalmol. 101:199, 1986.

11. Heijl, A., Lindgren, G., and Olsson, J.: Normal variability of static perimetric threshold values across the central visual field. Arch. Ophthalmol. 105:1544, 1987.

12. Katz, J., and Sommer, A.: A longitudinal study of the age-adjusted variability of automated visual fields. Arch. Ophthalmol. 105:1083, 1987.

13. Heijl, A.: Perimetric threshold variability and age. Arch. Ophthalmol. 106:450, 1988.

14. ———: Lack of diffuse loss of differential light sensitivity in early glaucoma. Acta Ophthalmol. 67:353, 1989.

15. Langerhorst, C. T., van den Berg, T. J. T. P., and Greve, E. L.: Is there general reduction of sensitivity in glaucoma? Int. Ophthalmol. 13:31, 1989.

16. Heijl, A., Lindgren, G., Olsson, J., and Asman, P.: Visual field interpretation with empirical probability maps. Arch. Ophthalmol. 107:204, 1989.

17. Heijl, A., and Asman, P.: A clinical study of perimetry probability maps. Arch. Ophthalmol. 107:199, 1989.

18. Flammer, J., Drance, S. M., Augustiny, L., and Funkhouser, A.: Quantification of glaucomatous visual field defects with automated perimetry. Invest. Ophthalmol. Vis. Sci. 26:176, 1985.

19. Wu, D. C., Schwartz, B., and Nagin, P.: Trend analyses of automated visual fields. In Greve, E. L., and Heijl, A. (eds.): Documenta Ophthalmologica Proceedings Series 49, Seventh International Visual Field Symposium. Dordrecht, Dr. W. Junk Publishers, 1987, pp. 175–189.

20. Chauhan, B. C., Drance, S. M., and Douglas, G. R.: The use of visual field indices in detecting changes in the visual field in glaucoma. Invest. Ophthalmol. Vis. Sci. 31:512, 1990.

21. Flammer, J., Drance, S. M., and Zulauf, M.: Differential light threshold. Short- and long-term fluctuation in patients with glaucoma, normal controls, and patients with suspected glaucoma. Arch. Ophthalmol. 102:704, 1984.

22. Heijl, A., Lindgren, A., and Lindgren, G.: Test-

retest variability in glaucomatous visual fields. Am. J. Ophthalmol. 108:130, 1989.

23. Werner, E. B., Petrig, B., Krupin, T., and Bishop, K. I.: Variability of automated visual fields in clinically stable glaucoma patients. Invest. Ophthalmol. Vis. Sci. 30:1083, 1989.

24. Flammer, J., and Bebie, H.: Lens opacity meter. A new instrument to quantify lens opacity. Ophthalmologica 195:69, 1987.

25. Goldstick, B. J., and Weinreb, R. N.: The effect of refractive error on automated global analysis program G-1. Am. J. Ophthalmol. 104:229, 1987.

26. Heuer, D. K., Anderson, D. R., Feuer, W. J., and Gressel, M. G.: The influence of refraction accuracy on automated perimetric threshold measurements. Ophthalmology 94:1550, 1987.

27. Werner, E. B., Adelson, A., and Krupin, T.: Effect of patient experience on the results of automated perimetry in clinically stable glaucoma patients. Ophthalmology 95:764, 1988.

LETTERS TO THE JOURNAL

Microwave Thermotherapy for Choroidal Hemangioma

Paul T. Finger, M.D., Robert W. Paglione, M.E.E., and Samuel Packer, M.D.

Division of Ocular Tumor and Orbital Disease, Department of Ophthalmology, North Shore University Hospital–Cornell University Medical College (P.T.F., S.P.), and David Sarnoff Research Center, Inc., SRI International (R.W.P.). Mr. Paglione has a proprietary interest in the microwave applicator.

Inquiries to Paul T. Finger, M.D., Department of Ophthalmology, North Shore University Hospital–Cornell University Medical College, 300 Community Dr., Manhasset, NY 11030.

Microwave hyperthermia (heat) has been used with iodine-125 plaque irradiation to treat patients with choroidal and ciliary body melanomas.[1] One of the reasons why heat was chosen as an adjuvant to radiation therapy was because low-level heating over time has been shown to be capable of causing vascular damage within a tumor.[2-4]

In treatment of choroidal hemangiomas, scatter photocoagulation has been used by Anand, Augsburger, and Shields[5] to reattach the retina in 19 of 24 eyes. Of these 24 eyes, ten (40%) required retreatment for recurrence of subretinal fluid. A good visual prognosis was believed to be maintainable in only 30% of cases. Scatter photocoagulation heats random spots on the surface of a leaking choroidal hemangioma. In contrast, episcleral application of a dish-shaped microwave plaque could preferentially heat the entire base of the tumor and therefore target its entire vascular supply (Figure).

We used the microwave applicator to treat a patient with a choroidal hemangioma. The construction and function of our microwave applicator has been previously described.[1] A 61-year-old women had a circumscribed choroidal hemangioma 8.0 × 8.0 mm in basal diameter, 3.2 mm in height, with its posterior margin 2.0 mm from her left fovea. Visual acuity was 20/40 in both eyes. The patient had been observed for 18 months when she returned with decreased vision. Ophthalmic examination disclosed visual acuity of L.E.: 20/100, a serous retinal detachment extending to the fovea, macular edema, and an exudate below the fovea. Ultrasonography disclosed an apical tumor spike of 4.4 mm and high intratumor reflectivity.

The risks and benefits of laser compared with microwave thermotherapy were discussed in

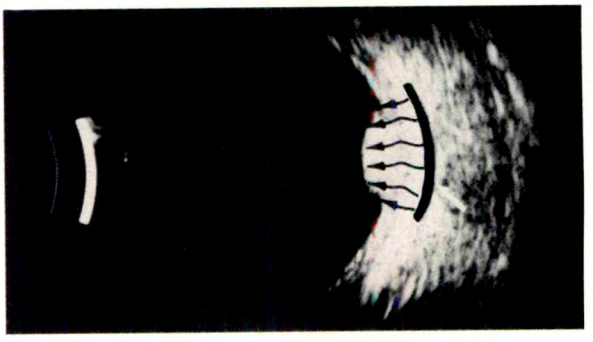


Figure (Finger, Paglione, and Packer). Ultrasonogram (transverse section) showing the choroidal hemangioma and the relative position and direction of heating (black arrows) provided by a microwave applicator drawn onto the photograph for demonstration (white arrow).

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

detail. The patient was informed that she would be the first patient treated with microwave thermotherapy for choroidal hemangioma. In an operative procedure the lateral rectus muscle was disinserted, and transillumination was performed to define the tumor margins. The edges of the tumor were marked on the sclera with tissue dye, then a dish-shaped microwave plaque was affixed to cover the entire base of the tumor. The 10.0-mm thermal zone was offset to avoid direct heating of the fovea. The tumor was heated to a field-off episcleral temperature of 47 C for 45 minutes.[2-4]

After microwave thermotherapy, visual acuity in the left eye was corrected to 20/50 at two months and 20/30 at six months. Two years after treatment, visual acuity decreased to 20/50. Ophthalmic examination showed a mild nuclear cataract, whereas fluorescein angiography showed diffuse intratumoral leakage, mild cystoid macular edema, and no new fluid extension to the fovea. The decreased visual acuity was attributed to a combination of the lenticular disease and macular edema.

In contrast with photocoagulation, episcleral microwave thermotherapy was a surgical procedure designed to heat the base of the tumor and therefore target its vascular supply in a more uniform fashion. Clearly, in cases in which there is a large retinal detachment and scatter photocoagulation is not possible, microwave thermotherapy offers an alternative to intraocular surgery, diathermy, or both.

References

1. Finger, P. T., Packer, S., Paglione, R. W., Gatz, J. F., Ho, T. K., and Bosworth, J. L.: Thermoradiotherapy of choroidal melanoma. Clinical experience. Ophthalmology 96:1384, 1989.

2. Dudar, T. E., and Jain, R. K.: Differential response of normal and tumor microcirculation to hyperthermia. Cancer Res. 44:605, 1984.

3. Song, C. W.: Effect of local hyperthermia on blood flow and microenvironment. A review. Cancer Res. 44:472, 1984.

4. Reinhold, H. S., and Endrich, B.: Tumor microcirculation as a target for hyperthermia. Int. J. Hyperthermia 2:111, 1986.

5. Anand, R., Augsburger, J. J., and Shields, J. A.: Circumscribed choroidal hemangiomas. Arch. Ophthalmol. 107:1338, 1989.

Disk Neovascularization in Chronic Anterior Uveitis

John M. Pach, M.D., David C. Herman, M.D., James A. Garrity, M.D., and Paul H. Kalina, M.D.

Department of Ophthalmology, Mayo Clinic and Mayo Foundation.

Inquiries to John M. Pach, M.D., Mayo Clinic and Mayo Foundation, 200 First St. S.W., Rochester, MN 55905.

Optic disk neovascularization is known to occur in chronic posterior inflammatory conditions.[1] It has been recently reported to occur in chronic iridocyclitis associated with juvenile rheumatoid arthritis.[2] We treated two patients with disk neovascularization and chronic anterior uveitis associated with the HLA-B27 haplotype who did not meet the diagnostic criteria for juvenile rheumatoid arthritis.[3]

Case 1

In August 1982, a 13-year-old girl had a one-year history of a smoldering anterior uveitis in the right eye, which was treated with topical, periocular, and oral corticosteroids. Visual acuity was 20/20 in each eye. The right eye had diffuse keratic precipitates, moderate anterior chamber cell and flare, and moderate anterior vitreous cells. The left eye was normal. Results of fundus examinations of both eyes were normal. Results of general medical examination were within normal limits, except for

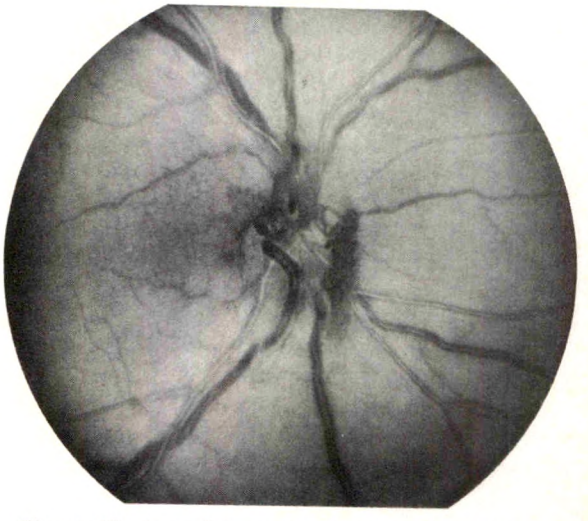


Fig. 1 (Pach and associates). Case 2, right eye. Recurrence of disk neovascularization in September 1988.

mild joint swelling of the left knee, which persisted for less than six weeks and did not recur. Laboratory results disclosed the presence of HLA-B27 antigen and negative results of an antinuclear antibody test. Despite topical and low-dose oral corticosteroids, a smoldering, low-grade anterior uveitis persisted in the right eye.

In April 1983, neovascularization was noted on the right disk. Fluorescein angiography showed no evidence of capillary nonperfusion posteriorly. As the inflammation subsided with topical therapy, the disk neovascularization regressed.

In January 1987, the patient developed a small, localized vitreous hemorrhage secondary to recurrent disk neovascularization that regressed after treatment with a periocular corticosteroid injection. She subsequently developed increased intraocular pressure, which persisted after three failed filtering procedures.

In January 1989, visual acuity was no light perception in the right eye because of glaucomatous optic atrophy.

Case 2

In January 1985, a 15-year-old girl had a one-year history of a smoldering uveitis in the left eye and a one-month history of iritis in the right eye. She had a history of low back pain with several hours of morning stiffness accompanied by stiffness in her hands, neck, and feet. Visual acuity was R.E.: 20/25 and L.E.: 20/30. Keratic precipitates were noted in both eyes, worse in the right eye. The anterior chambers were deep with moderate cells in the right eye and mild cells in the left eye. Extensive posterior synechiae were present in the left eye. Results of fundus examinations were unremarkable, except for mild anterior vitreous cells in the left eye. Laboratory testing disclosed the presence of HLA-B27 antigen, positive results of an antinuclear antibody test (1:640), and a nonreactive rheumatoid factor test. She was initially treated with systemic prednisone and topical corticosteroids with a favorable response.

In July 1987, the inflammation worsened with moderate cell and flare in the anterior chambers in both eyes. In October 1987, disk neovascularization developed in the right eye, which regressed with periocular and topical corticosteroids.

In September 1988, the disk neovascularization recurred in the right eye (Fig. 1) and regressed with topical corticosteroid therapy (Fig. 2). Fluorescein angiography demonstrated the neovascularization but did not show capillary nonperfusion posteriorly.

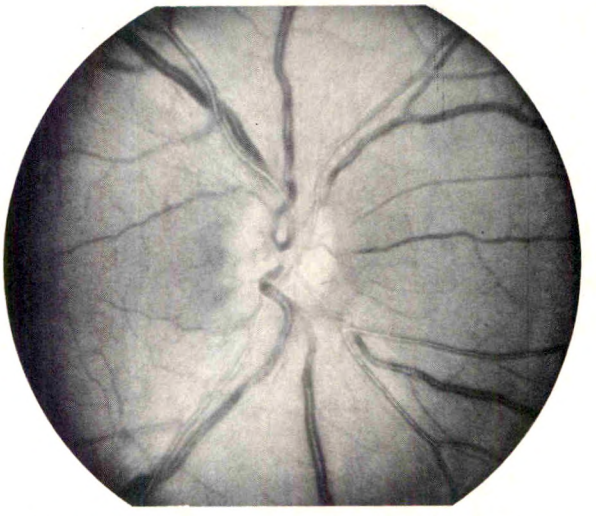


Fig. 2 (Pach and associates). Case 2, right eye. Regression of disk neovascularization after treatment with topical corticosteroids in November 1988.

In both of our patients, the inflammation was primarily confined to the anterior segment. Fluorescein angiography did not disclose capillary nonperfusion. In each patient, disk neovascularization responded to intensified medical therapy that reduced the ocular inflammation.[4] Neither patient met the accepted criteria for juvenile rheumatoid arthritis.[3] Severe anterior segment inflammation in children and young adults may promote posterior segment neovascularization regardless of the type of underlying systemic disease.

References

1. Shorb, S. R., Irvine, A. R., Kimura, S. J., and Morris, B. W.: Optic disk neovascularization associated with chronic uveitis. Am. J. Ophthalmol. 82:175, 1976.

2. Semple, H. C., Landers, M. B., III, and Morse, L. S.: Optic disk neovascularization in juvenile rheumatoid arthritis. Am. J. Ophthalmol. 110:210, 1990.

3. Cassidy, J. T., Levinson, J. E., Bass, J. C., Baum, J., Brewer, E. J., Jr., Fink, C. W., Hanson, V., Jacobs, J. C., Masi, A. T., Schaller, J. G., Fries, J. F., McShane, D., and Younge, D.: A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. Arthritis Rheum. 29:274, 1986.

4. Kelly, P. J., and Weiter, J. J.: Resolution of optic disk neovascularization associated with intraocular inflammation. Am. J. Ophthalmol. 90:545, 1980.

Retinal Vasculitis With Proliferative Retinopathy in a Patient With Evidence of *Borrelia burgdorferi* Infection

Gabriele E. Lang, M.D., Ulrich Schönherr, M.D., and Gottfried O. H. Naumann, M.D.

Department of Ophthalmology, University Eye Hospital.

Inquiries to Gabriele E. Lang, M.D., University Eye Hospital, Schwabachanlage 6, D-8520 Erlangen, Germany.

Lyme disease is an immune-mediated, multisystem disorder named after the first description of an endemic arthritis that occurred around Lyme, Connecticut.[1] Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is transmitted by the Ixodidae ticks.[2] The common symptoms are erythema migrans, oligoarthritis, and neurologic and cardiac abnormalities. Since patients may have ocular involvement in the second or third clinical stages, ophthalmologists should be aware of the ocular manifestations, such as conjunctivitis, iridocyclitis, retinal vasculitis, choroiditis, and optic neuritis.[3-5]

A 43-year-old man had a four-week history of blurred vision because of recurrent vitreous hemorrhage in the left eye. Visual acuity was 20/20 in both eyes. Intraocular pressure was 15 mm Hg in each eye by applanation tonometry. In the left eye, a corneal scar caused by a previous foreign body injury was noted. In both eyes, vitreous cells, vessel sheathing and occlusions, and patchy intraretinal hemorrhages were present. In the right eye, a small parafoveolar chorioretinal scar and a peripheral preretinal neovascularization at the 3 o'clock meridian were found at the border of a nonperfused area. In the left eye, vitreous hemorrhage and neovascularization at the optic nerve head, the superotemporal vascular arcade, and in the periphery at the 6 o'clock to 7 o'clock meridian were found. There was wrinkling of the inner retinal surface because of traction from the neovascularization (Fig. 1). Fluorescein angiography disclosed peripheral vessel closure with

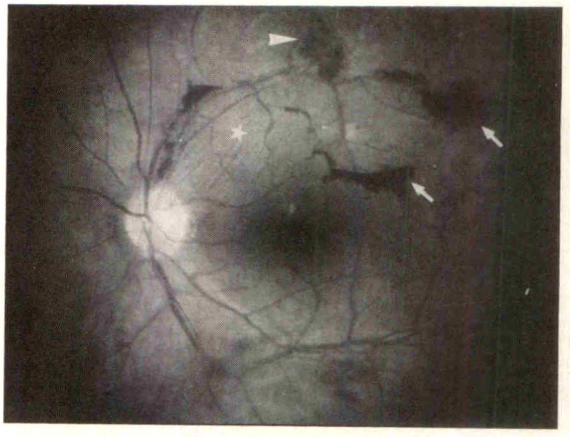


Fig. 1 (Lang, Schönherr, and Naumann). Vitreous hemorrhage (arrows), preretinal neovascularization (arrowhead), and wrinkling of the inner retinal surface (star).

areas of nonperfusion in both eyes. Leakage of dye was found from the neovascularization (Fig. 2).

The patient remembered having a tick bite one year previously. He also had pain in the joint of his right knee and in his wrists. On physical and X-ray examinations, sarcoidosis was ruled out, supported by an angiotensin-converting enzyme level of 19 U/ml. Differential blood cell count showed a slight leukocytosis of 12,600/nl. Results of laboratory tests for HLA-B27 were positive. The indirect Coombs' test for free serum antibodies was negative. Results of tests for DNA antibodies, anticytoplasmic antibodies, and antiphospholipid antibodies were negative. The results of serologic

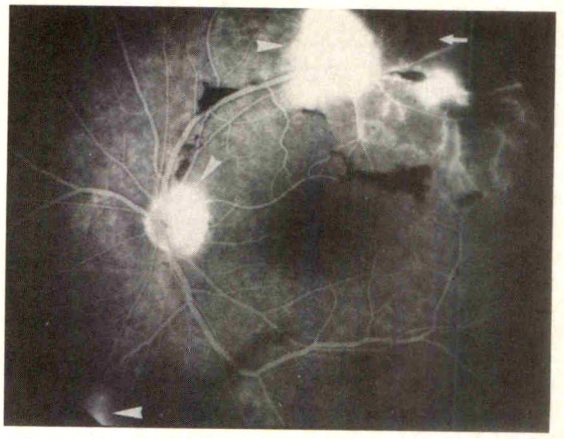


Fig. 2 (Lang, Schönherr, and Naumann). Corresponding fluorescein angiogram showing large areas of nonperfusion (arrow) and leakage of dye from the neovascularization at the optic disk and retina (arrowheads).

tests for herpes simplex, rubella, coxsackie virus, cytomegalovirus, *Yersinia* species, *Salmonella* species, *Treponema pallidum*, and human immunodeficiency virus were negative. Epstein-Barr virus IgG immunofluorescence test was 1:160, the test for IgM was negative, and *Toxoplasma gondii* immunofluorescence test was 1:64, which indicated a previous Epstein-Barr virus and *Toxoplasma* species infection. Results of the Lyme IgG immunofluorescence test were positive with 1:1280 (normal, less than 1:80); IgM was 1:10 (normal, less than 1:20).

The patient was treated with 200 mg of doxycyclin twice daily for two weeks. Lyme IgG titer thereafter decreased to 1:320 and IgM level was less than 1:10, which indicated sufficient treatment. The vessel sheathing, intraretinal hemorrhages, and arthralgia resolved within four weeks. We performed a focal laser treatment of the preretinal neovascularization in the right eye and a panretinal laser treatment in the left eye. In the right eye, the neovascularization was obliterated. In the left eye, recurrent vitreous hemorrhage occurred despite laser treatment with intermittent visual deterioration. The clinical course (rapid improvement of retinal vasculitis and arthralgia) and the decrease of the serum Lyme IgG titer after antibiotic therapy strongly indicated an infection with *B. burgdorferi* as the cause of the symptoms. In patients with retinal vaculitis, Lyme disease must be considered under the etiologic differential diagnosis.

References

1. Steere, A. C., Snydman, D. R., Shope, R. E., Andiman, W. A., Ross, M. R., and Steel, F. M.: Lyme arthritis. An epidemic of oligoarticular arthritis in children and adults in three Connecticut communities. Arthritis Rheum. 20:7, 1977.

2. Burgdorfer, W., Barbour, A. G., Hayes, S. F., Benach, J. L., Grunwaldt, E., and Davis, J. P.: Lyme disease. A tick-borne spirochetosis? Science 216:1317, 1982.

3. Aaberg, T. M.: The expanding ophthalmologic spectrum of Lyme disease. Am. J. Ophthalmol. 107:77, 1989.

4. Bialasiewicz, A. A., Ruprecht, K. W., Naumann, G. O. H., and Blenk, H.: Bilateral diffuse choroiditis and exudative retinal detachments with evidence of Lyme disease. Am. J. Ophthalmol. 105:75, 1988.

5. Schönherr, U., Lang, G. E., and Meythaler, F. H.: Bilaterale Leber'sche Neuroretinitis stellata bei *Borrelia burgdorferi* Serokonversion. Klin. Monatsbl. Augenheilkd. In press.

Peripheral Ulcerative Keratitis Related to Lyme Disease

Vincent P. deLuise, M.D., F.A.C.S., and Michael J. O'Leary, M.D.

Cornea Service, OptiCare Eye Health Center (V.P.d.L.), and Putnam Hospital (M.J.O.).

Inquiries to Vincent P. deLuise, M.D., F.A.C.S., Cornea Service, OptiCare Eye Health Center, 87 Grandview Ave., Waterbury, CT 06708.

Reported ocular findings in Lyme disease include conjunctivitis, papilledema with retinal hemorrhages, ischemic optic neuropathy, cranial nerve palsies, iritis, choroiditis, exudative retinal detachments, and nummular and interstitial keratitis.[1-4] We treated a patient with peripheral ulcerative keratitis presumed secondary to Lyme disease.

A 59-year-old woman had a tick bite on the left calf in June 1988 and subsequently developed a ring-shaped skin rash and migratory arthritis. She developed irritation and discomfort in the left eye in March 1989. The patient was examined on April 7, 1989, and was found to have an area of peripheral ulcerative keratitis in the nasal aspect of the left cornea with surrounding perilimbal vascularization, epithelial defect, and stromal infiltrate (Figure). Visual acuity was R.E.: 20/25 and L.E.: 20/25. Corneal scrapings plated on sheep blood agar, chocolate agar, and Sabouraud's medium resulted in no growth at 48 hours. An enzyme-linked immunosorbent assay for Lyme disease by optical density was positive at .151. Results of serologic tests for VDRL–fluorescent treponemal antibody absorption, antinuclear antibody, rheumatoid factor, and cryoglobulin were negative. The patient was treated with topical tobramycin and dexamethasone, and 2 g of intravenous cefuroxime daily for two weeks. The peripheral ulcerative keratitis gradually healed with an epithelialized facet and stromal thinning adjacent to a vascularized limbal scar. The systemic symptoms improved considerably. The patient had recurrent flare-ups of migratory arthritis that were treated with systemic cefazolin and prednisone. She was admitted to the hospital in December 1989 for severe arthritis and vasculitis, and a regimen of azathioprine was begun. The patient was last examined on June 4, 1990. Visual acuity was R.E.: 20/20 and L.E.: 20/20. The left corneal ulcer had healed with a vascularized scar and an intact epithelium. The patient was using nonpreserved artificial tear lubricants to the left eye four times a day, oral prednisone, and azathioprine.

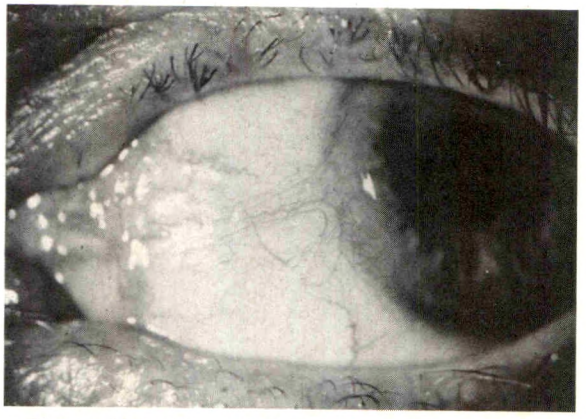


Figure (deLuise and O'Leary). Peripheral ulcerative keratitis with perilimbal vascularization of left eye.

Corneal involvement in Lyme disease can take a number of forms. Multiple, focal, nebular opacities at varying levels of the stroma have been described.[1-4] Sectoral corneal edema, neovascularization with scarring, and occasionally an accompanying keratouveitis have also been described.[3]

The mechanism of peripheral ulcerative keratitis reported in our case is most likely related to antigen-antibody deposition in the limbal stroma with release of complement secondary to vasculitis of the adjacent perilimbal and intrascleral blood vessels. Reported findings in Lyme disease of hemiparesis, infarction, and endarteritis are consistent with vasculitis similar to Wegener's granulomatosis.[5] Our patient's hospitalization in December 1989 resulted from a clinical diagnosis of vasculitis. We do not believe that direct ocular infection was the cause, as results of microbiologic cultures and VDRL–FTA-ABS serologic tests were negative. Other diseases, such as mumps, infectious mononucleosis, and herpes simplex, can produce an interstitial keratitis, but there was no clinical evidence to suggest any of these entities. Systemic vasculitis secondary to connective tissue disease can cause peripheral ulcerative keratitis, but serologic tests were negative.

As Baum and associates[1] described, episodic recurrences of clinical activity in syphilis are believed to be related to the persistence of antigen either as living organisms or fragments of organisms in treated patients. A similar mechanism may obtain in Lyme disease.[1] The Lyme spirochete could act as an antigenic trigger for a complement-mediated vasculitic event at the corneoscleral limbus, an immunologically active site. In our patient, the peripheral corneal ulcer developed and intensified during a period of known Lyme arthritis and vasculitis, and it resolved promptly once the serologic diagnosis was confirmed and intensive systemic antibiotic treatment was initiated. Therefore, we believe that peripheral ulcerative keratitis must be added to the ever-broadening spectrum of ocular findings in Lyme disease.

References

1. Baum, J., Barza, M., Weinstein, P., Groden, J., and Aswad, M.: Bilateral keratitis as a manifestation of Lyme disease. Am. J. Ophthalmol. 105:75, 1988.
2. Kornmehl, E. W., Lesser, R. L., Jaros, P., Rocco, E., and Steere, A. C.: Bilateral keratitis in Lyme disease. Ophthalmology 96:1194, 1989.
3. Orlin, S. E., and Lauffer, J. L.: Lyme disease keratitis. Am. J. Ophthalmol. 107:678, 1989.
4. Bertuch, A. W., Rocco, E., and Schwartz, E. G.: Lyme disease. Ocular manifestations. Ann. Ophthalmol. 20:376, 1988.
5. Reik, L.: *Borrelia burgdorferi* infection. A neurologist's perspective. Ann. N. Y. Acad. Sci. 539:1, 1988.

Malignant Glaucoma After Nd:YAG Cyclophotocoagulation

David R. Hardten, M.D., and J. David Brown, M.D.

Department of Ophthalmology, University of Minnesota School of Medicine.

Inquiries to J. David Brown, M.D., Department of Ophthalmology, University of Minnesota School of Medicine, Box 493, Minneapolis, MN 55455.

Nd:YAG cyclophotocoagulation is being used increasingly in the treatment of refractory glaucoma. It appears to be both effective and relatively safe, although complications such as corneal edema, hyphema, cataract formation, recurrent retinal detachment, hypotony and choroidal effusion, and vitreous hemorrhage have been described in association with this procedure.[1] We treated a patient who developed malignant glaucoma after Nd:YAG cyclophotocoagulation.

A 39-year-old woman was referred to our institution for treatment of aphakic uveitic glaucoma in her left eye that was unresponsive to maximal medical treatment. She had a history of chronic iridocyclitis in the left eye, extracapsular cataract extraction without an intraocular lens, trabeculectomy and peripheral

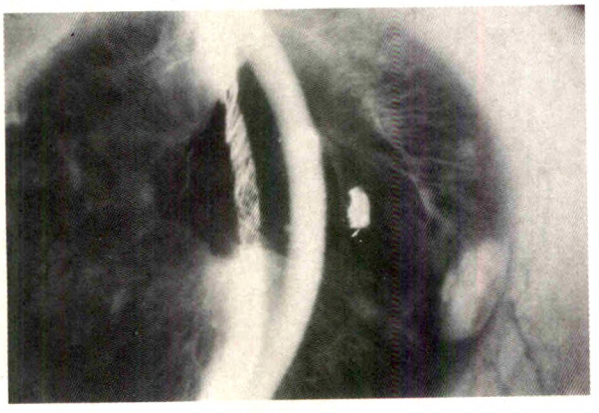


Fig. 1 (Hardten and Brown). Appearance of eye before Nd:YAG hyaloidotomy showing a shallow anterior chamber.

iridectomy, bleb revision, and cyclocryotherapy. Results of examination of the right eye were unremarkable. Best-corrected visual acuity was 20/30 in the left eye. Intraocular pressure was 32 mm Hg. No bleb was identified, and there was no inflammation. A patent basal surgical iridectomy was present at the 11 o'clock meridian, and the anterior chamber was deep. The posterior capsule was intact, and scattered synechiae of the iris to the posterior capsule were present. The cup/disk ratio was 0.7.

Informed consent was obtained from the patient. After pretreatment with flurbiprofen and dexamethasone and injection of retrobulbar anesthesia, the patient received 20 spots at 8.6 J to the inferior 150 degrees of the left eye, 1.5 mm posterior to the corneoscleral limbus, using a Nd:YAG laser in the free-running, thermal mode with a duration of 20 milliseconds and with a retrofocus of 3.6 mm. One hour postoperatively, the anterior chamber depth was unchanged and intraocular pressure was 26 mm Hg.

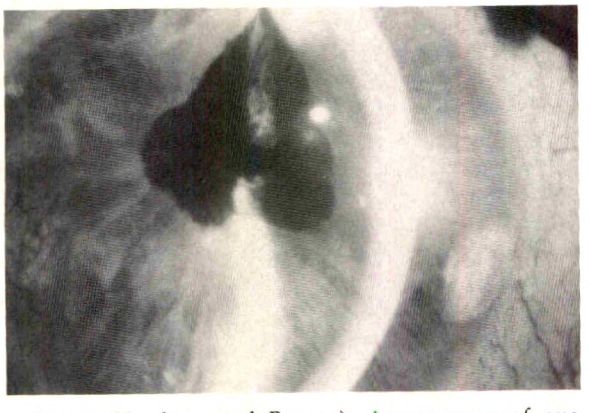


Fig. 2 (Hardten and Brown). Appearance of eye after Nd:YAG hyaloidotomy showing the immediate and marked anterior chamber deepening.

The patient was treated with atropine 1% twice daily, dexamethasone 0.1% four times daily. Intraocular pressure fluctuated between 22 and 44 mm Hg, and the anterior chamber progressively became more shallow over the next two weeks. When we again examined the patient two weeks after the initial procedure, visual acuity was 20/40 and intraocular pressure was 44 mm Hg in the left eye. The anterior chamber was shallow centrally, with iris-to-cornea touch peripherally (Fig. 1). There was only mild anterior chamber inflammation. The opacified posterior capsule was bowed forward. There was no choroidal effusion detectable.

At this point, the Nd:YAG laser in the Q-switched mode was used to make a central opening in the posterior capsule and disrupt the anterior hyaloid face. The anterior chamber immediately deepened, and intraocular pressure decreased to 26 mm Hg (Fig. 2). Over the next few weeks, the anterior chamber remained deep, but intraocular pressure continued to be inadequately controlled. This was treated with further Nd:YAG cyclophotocoagulation. Two months later, intraocular pressure was 14 mm Hg, and the examination results and visual acuity remained unchanged.

Malignant glaucoma, or posterior aqueous diversion, is a term used to describe a condition characterized by a shallow anterior chamber with increased intraocular pressure despite a patent iridectomy.[2-4] We believe the inflammation provoked by this procedure likely caused swelling and engorgement of the ciliary processes, which has been reported to cause central and anterior movement of the processes placing them in apposition with the peripheral anterior hyaloid.[3] This configuration could lead to a situation where aqueous humor is diverted posteriorly into the vitreous. The prompt response to anterior hyaloidotomy, as described by Epstein, Steinert, and Puliafito,[5] further substantiates this diagnosis. Nd:YAG cyclophotocoagulation represents a likely precipitating cause of the malignant glaucoma in this patient. The possibility of malignant glaucoma as a complication of Nd:YAG cyclophotocoagulation should be kept in mind, especially as the procedure becomes more commonly performed.

References

1. Hampton, C., Shields, M. B., Miller, K. N., and Blasini, M.: Evaluation of a protocol for transscleral

Neodymium:YAG cyclophotocoagulation in one hundred patients. Ophthalmology 97:910, 1990.
2. Luntz, M. H., and Rosenblatt, M.: Malignant glaucoma. Surv. Ophthalmol. 32:73, 1987.
3. Weiss, D. I., and Schaffer, R. N.: Ciliary block (malignant) glaucoma. Trans. Am. Acad. Ophthalmol. Otolaryngol. 76:450, 1972.
4. Levene, R. Z.: Current concepts of malignant glaucoma. Ophthalmic Surg. 17:515, 1986.
5. Epstein, D. L., Steinert, R. F., and Puliafito, C. A.: Neodymium-YAG laser therapy to the anterior hyaloid in aphakic malignant (ciliovitreal block) glaucoma. Am. J. Ophthalmol. 98:137, 1984.

Intracameral Tissue Plasminogen Activator for Resolution of Fibrin Clots After Glaucoma Filtering Procedures

Ramesh C. Tripathi, M.D., Brenda J. Tripathi, Ph.D., James K. Park, Ph.D., Luciano Quaranta, M.D., Kenneth Steinsapir, M.D., Erica Lehman, M.D., and J. Terry Ernest, M.D.

Department of Ophthalmology and Visual Science, University of Chicago.

Inquiries to Ramesh C. Tripathi, M.D., Visual Sciences Center, University of Chicago, 939 E. 57th St., Chicago, IL 60637.

The formation of fibrin clots in the anterior chamber of the eye after filtering procedures for glaucoma is a well-recognized complication that contributes to failure of surgery and to a compromise of the structural and functional integrity of the eye. Tissue plasminogen activator has been used for the rapid lysis of fibrin clots after vitrectomy and keratoplasty, as well as for the dissolution of a blood clot in conjunctival filtering blebs.[1] We applied tissue plasminogen activator for the treatment of massive fibrin clots in the anterior chamber and the associated obstruction of the sclerectomy filtering sites in two patients.

Under sterile conditions, we prepared the injectable solution by reconstituting 20 mg of lyophilized recombinant tissue plasminogen activator in 20 ml of distilled water. Multiple aliquots of 50 µl each were drawn into individual tuberculin syringes, capped, and stored at −90 C. Immediately before injection, the tissue plasminogen activator was warmed to room temperature, and a 30-gauge needle was attached to the syringe.

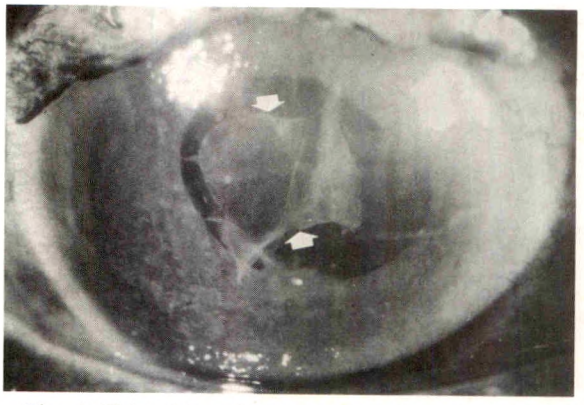


Fig. 1 (Tripathi and associates). Case 1. Anterior segment before injection of tissue plasminogen activator. An irregular sheet of fibrin clot (arrows) occupies the central area of the semidilated pupil and attaches to the pupillary margin, to the surface of the iris, and to posterior synechiae. Strands of fibrin also extend to the posterior surface of the cornea.

Case 1

A 69-year-old black woman underwent an uncomplicated extracapsular cataract extraction with intraocular lens implantation and revision of a posterior lip sclerectomy for primary open-angle glaucoma in the right eye. Postoperatively, the patient received intensive topical corticosteroid and cycloplegic therapy. Nevertheless, during Days 3 through 5, a large sheet of fibrin clot appeared in the anterior chamber (Fig. 1). Concurrently, the conjunctival bleb became flat and intraocular pressure increased from 2 to 21 mm Hg. On Day 6, we injected 15 µg of tissue plasminogen activator into the right anterior chamber. Within 30 minutes, the fibrin clot dissolved completely, and the filtering bleb became elevated (Fig. 2). By 45 minutes, the intraocular pressure decreased from 24 to 12 mm Hg, and it has remained stable during six weeks of follow-up. A cystic bleb and a clear anterior chamber and cornea have also been maintained.

Case 2

An 87-year-old black woman underwent an uncomplicated extracapsular cataract extraction with intraocular lens implantation combined with posterior lip sclerectomy and peripheral iridectomy for primary open-angle glaucoma in the right eye. On the fifth postoperative day, despite conventional medical therapy, a large fibrin clot formed in the anterior

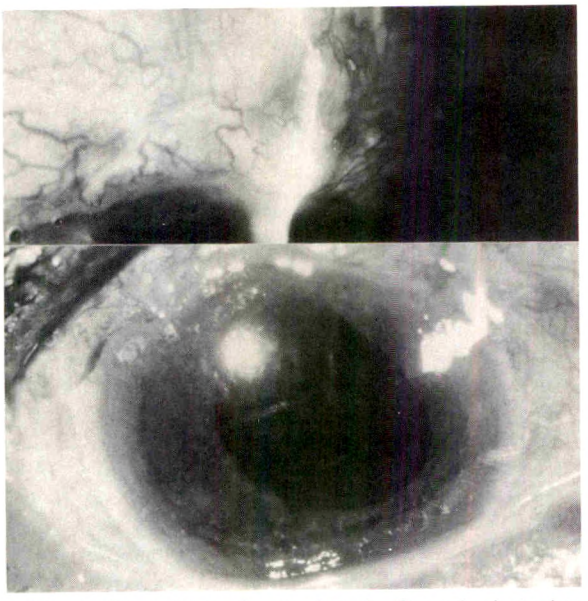


Fig. 2 (Tripathi and associates). Case 1. Anterior segment after 30 minutes of intracameral injection of 15 μl of tissue plasminogen activator. The fibrin clot and posterior synechiae are lysed completely, and the anterior chamber and the pupillary area are optically clear (bottom). Superiorly, the conjunctival bleb, corresponding to the site of sclerectomy, is elevated (top).

chamber, the filtering bleb flattened, and intraocular pressure was 22 mm Hg. On Day 6, after aspirating 30 μl of aqueous, we injected 25 μg of tissue plasminogen activator into the anterior chamber. Within 25 minutes, the fibrin clot had dissolved completely, and intraocular pressure was 18 mm Hg. The next day, the bleb was large and cystic, and intraocular pressure was 3 mm Hg. A 10% hyphema was present, but this resolved within two days, and intraocular pressure stabilized at 14 mm Hg. After three months of follow-up, the condition of the eye remained stable, with a cystic bleb and a clear anterior chamber and cornea.

Filtration procedures for glaucoma often fail because of scarring at the surgical site. Fibrin clots that occur two to five days after such procedures provide a scaffold for the formation of scar tissue in the anterior chamber and in the fistulization tract. Our results indicate that intracameral injection of tissue plasminogen activator for dissolution of fibrin clot is an effective and safe procedure that minimizes the complications induced by the clot and, hence, the early failure of glaucoma surgery.

Reference

1. Ortiz, J. R., Walker, S. D., McManus, P. E., Martinez, L. A., Brown, R. H., and Jaffe, G. J.: Filtering bleb thrombolysis with tissue plasminogen activator. Am. J. Ophthalmol. 106:624, 1988.

Candida albicans Corneal Ulcer Associated With Crack Cocaine

Bruce M. Zagelbaum, M.D., Mark H. Tannenbaum, M.D., and Peter S. Hersh, M.D.

Department of Ophthalmology, Bronx-Lebanon Hospital Center, Albert Einstein College of Medicine.

Inquiries to Peter S. Hersh, M.D., Department of Ophthalmology, Bronx-Lebanon Hospital Center, 1650 Selwyn Ave., Bronx, NY 10457.

The use of crack cocaine has been implicated in the development of nontraumatic corneal epithelial defects.[1,2] We treated a patient who smoked crack cocaine regularly and developed a fungal *Candida albicans* corneal ulcer.

A 27-year-old woman had lacrimation, injection, and photophobia in her left eye for two weeks. She had smoked crack cocaine every day for eight months. Best-corrected visual acuity was R.E.: 20/20 and L.E.: 20/50+. On slit-lamp examination, the left eye had a 1.5-mm central corneal infiltrate with 50% stromal thinning. The anterior chamber had a moderate cellular reaction and a 2.0-mm hypopyon. Corneal sensation was markedly decreased. Tear breakup time was less than five seconds, and results of Schirmer's testing with topical anesthesia were R.E.: 5.0 mm and L.E.: 10.0 mm after five minutes.

Cultures were taken on blood, chocolate, and Sabouraud's dextrose agar. A Gram stain showed no organisms. Treatment was begun immediately with hourly fortified gentamicin sulfate eyedrops (14 mg/ml), fortified cefazolin eyedrops (100 mg/ml), and cycloplegics. On Day 3, cultures all grew *Candida albicans*. The patient was, therefore, started on a regimen of natamycin 5% eyedrops every hour in addition to the antibiotic eyedrops.

On Day 8, the size of the infiltrate remained unchanged, and the hypopyon had resolved (Fig. 1). The patient continued taking natamycin eyedrops, and the antibiotics were dis-

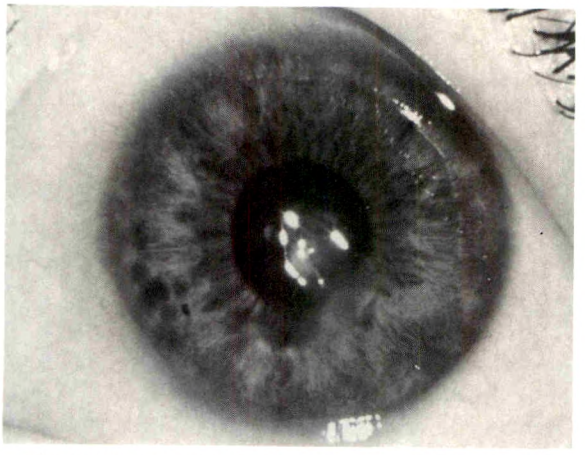


Fig. 1 (Zagelbaum, Tannenbaum, and Hersh). *Candida albicans* corneal ulcer associated with the use of crack cocaine. Central stromal thinning (50%) is present.

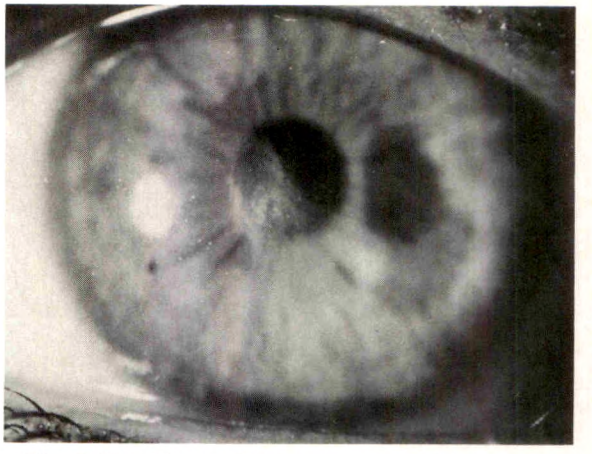


Fig. 2 (Zagelbaum, Tannenbaum, and Hersh). Resolved *Candida albicans* corneal ulcer.

continued. On Day 18, however, the infiltrate had enlarged to 1.5 × 3.5 mm with 50% stromal thinning and a new 1.0-mm adjacent corneal ulcer was present. Cultures were taken, which again grew *Candida albicans*. Treatment was started with miconazole 1% and flucytosine 1% solutions alternating every hour and 1.5 g of flucytosine orally four times daily. The miconazole and flucytosine eyedrops were continued for five weeks with resolution of the infiltrate and complete reepithelialization. At the three-month follow-up examination, the cornea had a 1.5 × 3.5-mm scar partially over the visual axis with 50% stromal thinning (Fig. 2). Final visual acuity was R.E.: 20/20 and L.E.: 20/20.

Keratomycosis is most common in patients with chronic disease, in diseased corneas with abnormal epithelium, and in those treated with long-term corticosteroids.[3,4] Fungal corneal ulcers have also been reported to occur in association with acquired immunodeficiency syndrome.[5]

We hypothesize that use of crack cocaine may predispose an otherwise healthy patient to infectious keratitis. A number of possible mechanisms may account for this susceptibility. First, epithelial changes induced directly by crack cocaine smoke may decrease the barrier effect of the epithelium toward invasive organisms.[2] These changes may be toxic or neurotrophic in origin or could conceivably represent a subclinical alkali burn, given the alkaline nature of crack cocaine. Furthermore, the local anesthesia induced by crack cocaine may disrupt normal blink mechanisms and cause an exposure keratopathy, predisposing toward subsequent infection. Physicians should be aware of this subset of patients with infectious keratitis who may not have any other risk factors for corneal infection.

References

1. McHenry, J. G., Zeiter, J. H., Madion, M. P., and Cowden, J. W.: Corneal epithelial defects after smoking crack cocaine. Am. J. Ophthalmol. 108:732, 1989.

2. Brewitt, H., Bonatz, E., and Honegger, H.: Morphological changes of the corneal epithelium after application of topical anesthetic ointments. Ophthalmologica 180:198, 1980.

3. Thygeson, P., and Okumoto, M.: Keratomycosis. A preventable disease. Trans. Am. Acad. Ophthalmol. Otolaryngol. 78:433, 1974.

4. Forster, R. K., and Refell, G.: The diagnosis and management of keratomycosis. Arch. Ophthalmol. 93:975, 1975.

5. Parrish, C. M., O'Day, D. M., and Hoyle, T. C.: Spontaneous fungal corneal ulcer as an ocular manifestation of AIDS. Am. J. Ophthalmol. 104:302, 1987.

Ketoprofen in the Treatment of Scleritis

David C. Medway, B.A., Deborah M. Donzis, R.N., and Paul B. Donzis, M.D.

Department of Ophthalmology, George Washington University School of Medicine (D.C.M.), and Department of Ophthalmology, Jules Stein Eye Institute, UCLA School of Medicine (D.M.D., P.B.D.).

Inquiries to David C. Medway, B.A., 2401 H. St. N.W., Ste. 805, Washington, DC 20037.

Scleritis is an inflammation of the sclera, which may occur as anterior or posterior, diffuse or nodular, or necrotizing or nonnecrotizing disease.[1] Systemic noncorticosteroidal antiinflammatory agents have been the traditional first-line therapeutic agents in cases of nonnecrotizing disease.[2] Indomethacin and flurbiprofen have proven effective.[1,2]

We treated two patients with nonnecrotizing diffuse scleritis that responded to ketoprofen, a noncorticosteroidal antiinflammatory drug that also has excellent analgesic properties.[3,4]

Case 1

A 47-year-old man had a ten-day history of a painful, red right eye. Initial ophthalmic examination disclosed severe vascular injection localized to the lateral quadrant of the right eye. No evidence of vascular closure or scleral destruction was present. Episcleritis was the initial diagnosis, and the patient was given topical prednisolone sulfate 1% and 200 mg of ibuprofen orally every six hours. Four days later there were no signs of clinical improvement. Localized tenderness was present, and a diagnosis of diffuse nonnecrotizing scleritis was made. The patient was given 75 mg of ketoprofen three times a day. The other medications were discontinued. Within 24 hours the patient had complete relief of pain. Three days later the area of vascular injection was markedly reduced. The patient continued to improve over the next two weeks and the ketoprofen was tapered without recurrence of the disease.

Case 2

A 53-year-old woman had an 11-day history of a red, painful left eye. The patient had rheumatoid arthritis that was treated with 50 mg of flurbiprofen three times a day. Ophthalmic examination disclosed severe vascular injection over the lateral quadrant of the left eye. There was localized tenderness as well as scleral and episcleral edema in this area. A diagnosis of scleritis was made, and the patient was given 50 mg of ketoprofen three times a day. At the same time, the flurbiprofen was discontinued. The patient stated that she had relief of pain within the 24 hours, and five days later the eye was completely asymptomatic. The ketoprofen was tapered over the next week and then flurbiprofen was resumed for the treatment of her arthritis.

Scleritis often manifests with vascular injection, tissue edema, and pain, as demonstrated by the findings in our two patients. Scleritis may occur as a localized process, or it may be associated with systemic collagen vascular disease, such as rheumatoid arthritis.[1]

Ketoprofen, unlike most other noncorticosteriodal antiinflammatory agents, has a potent inhibitory action on both the cyclooxygenase pathway and the lipooxygenase pathway of the arachidonic acid cascade.[5] This latter pathway produces noncyclized monohydroxy acids and leukotrienes, which mobilize leukocytes and increase vascular permeability, thereby promoting edema. This ability to act effectively on both pathways of arachidonic acid metabolism may be useful in treating inflammatory conditions. Ketoprofen is also an effective analgesic equivalent in efficacy to 650 mg of acetaminophen plus 60 mg of codeine.[4] Both of our patients were being treated with other noncorticosteroidal agents without improvement before being given ketoprofen. The response, however, to noncorticosteroidal antiinflammatory agents may vary with each patient.[1]

Current recommended initial starting dosage for ketoprofen is 75 mg three times a day. Potential side effects include gastrointestinal and renal toxicity. Ketoprofen, with its excellent analgesic and antiinflammatory actions, appears well suited as a therapeutic agent in the treatment of scleritis.

References

1. Watson, P. G.: Diseases of the sclera and episclera. In Tasman, W., and Jaeger, E. A. (eds.): Duane's Clinical Ophthalmology, vol. 4, chap. 23. Philadelphia, J. B. Lippincott, 1989, pp. 1–43.

2. ———: The diagnosis and management of scleritis. Ophthalmology 87:716, 1980.

3. Fossgreen, J., and Brown-Thomsen, J.: Ketoprofen. A new nonsteroidal anti-inflammatory agent. Scand. J. Rheumatol. 5:7, 1976.

4. Sunshine, A., and Olson, N. Z.: Analgesic efficacy of ketoprofen in postpartum, general surgery, and chronic cancer pain. J. Clin. Pharmacol. 28:S47, 1988.

5. Walker, J. L.: Interrelationships of SRS-A production and arachidonic acid metabolism in human lung tissue. Adv. Prostaglandin Thromboxane Res. 6:115, 1980.

Repair of a Giant Scleral Ulcer With a Scleral Graft and Tissue Glue

Chang Ping Lin, M.D., Yuh Hsin Wu, M.D., Ming Tsong Chen, M.D., and Wen Loong Huang, M.D.

Department of Ophthalmology, Kaohsiung Medical College.

Inquiries to Chang Ping Lin, M.D., Department of Ophthalmology, Kaohsiung Medical College, Kaohsiung, Taiwan, Republic of China.

A 65-year-old man had severe scratchiness in his right eye for two weeks. The ophthalmic examination disclosed an edematous cornea, hypopyon, irregular pupil, and an infiltrated ulcer covered with calcified deposits at the nasal sclera surrounded by congested conjunctiva. Movement of the globe toward the nasal side was restricted. Best-corrected visual acuity was R.E.: 20/100. The patient had a pterygium excised at the ulcer site six years previously.[1] Endophthalmitis originating from the scleral ulcer was diagnosed.

After admission, 1% amikacin sulfate and 5% cephradine eyedrops were applied alternately at one-hour intervals initially and reduced to two-hour intervals. Irrigation for the ulcer and adjacent subconjunctival space with 1% amikacin sulfate was performed daily. A subconjunctival abscess was treated with repeated conjunctival dissection and débridement. The bacterial culture showed *Pseudomonas aeruginosa*. After the ocular discharge decreased and the infection subsided, a scleral graft was planned.

The scleral graft began with the conjunctival dissection and necrotic scleral débridement. There was little obvious demarcation between healthy and necrotic sclera. An area approximately 210 degrees from the 10 o'clock to the 5 o'clock meridian was débrided, which exposed uveal tissue in most of this area. Both donor and recipient sites were cleaned and dried. Tissue glue was applied diffusely on the recipient site. The transplant tissue was placed promptly on the recipient site, and slight pressure was applied on the graft by forceps to ensure its adhesion. No suture was used in the scleral graft. The conjunctival defect was apposed with a conjunctival graft from the fellow eye and fixed with a continuous 10-0 nylon suture. Six days later, new infectious foci were found at the lower and temporal parts of the eye. The same procedure was repeated with the tissue glue applied in dots instead of diffusely. The second graft was encircled from the 6 o'clock to approximately the 10 o'clock meridian. The entire scleral graft involved more than 300 degrees.

After six months of follow-up, the graft healed well. The anterior chamber was clear, and no choroidal or retinal degeneration was detected. Despite a mild cataract, final best-corrected visual acuity was 20/40. The only complication was grittiness caused by the protruding glue. The blue, transparent, hard tissue glue emerged through the conjunctiva in dots or pieces, but it could be removed easily.

Since the scleral tissue around the ulcer area was necrotic and edematous, tissue cutting prevented the possibility of suturing. Because the large scleral ulcer extended far from the corneoscleral limbus and around the corneoscleral limbus for more than 300 degrees, suturing the graft would be bothersome and time consuming. Tissue glue application is a simple, fast, and effective method to fix giant scleral grafts.

Reference

1. Su, M. Y., Chung, C. B., Chen, C. W., Wu, W. C., and Jeng, Y. M.: Scleral ulcer after pterygium excision. Trans. Soc. Ophthalmol. China 23:124, 1984.

Retained Veirs Rod and Canaliculitis

Bruce B. Becker, M.D.

Jules Stein Eye Institute, and Department of Ophthalmology, UCLA School of Medicine.

Inquiries to Bruce B. Becker, M.D., 5363 Balboa Blvd., Ste. 246, Encino, CA 91316.

Lacrimal stents are frequently used in the treatment of canalicular lacerations and stenosis.[1] If the stents are not removed or are removed incompletely, there is potential for complications.[2-5]

A 73-year-old woman, referred in September 1989, had a history of left-sided epiphora for 15 years and previous episodes of apparent dacryocystitis for one year. She was treated in 1975 for punctal stenosis with a left inferior punctal snip procedure performed with placement of a Veirs rod in the left inferior canaliculus. According to the clinical record, on follow-up examination the next day the Veirs rod was

gone. In March 1977, a pyrex tube was placed without a dacryocystorhinostomy. In 1981, an infection was noted around the tube. The tube was replaced several times until it was removed in 1983.

Examination showed left-sided epiphora. There was erythema and edema of the left inferior canaliculus and reflux of purulence with pressure over the canaliculus. Passage of a probe and irrigation could be accomplished through the left inferior canaliculus into the nose. Cultures grew *Enterobacter* and *Klebsiella* species. Because of the history of multiple lacrimal procedures and possible dacryocystitis, a left dacryocystorhinostomy was performed. During surgery, a 7-mm corroded metal rod was removed from the distal left inferior canaliculus. Symptoms resolved and the patient had a patent lacrimal excretory system after the operation.

Veirs rods have been used as stents for canalicular lacerations, although silicone tubing has become the preferred stent in recent years.[1] Because of their short length, Veirs rods have the potential to be lost in the lacrimal system, especially if the attached silk suture is cut short or becomes detached. Mensher and Leibsohn[2] reported a case in a child in which a Veirs rod slid down the nasolacrimal duct and was ingested.

Retained canalicular stents may be associated with infection. Rootman, Insler, and Wolfley[3] reported a case of *Mycobacterium chelonae* canaliculitis after silicone intubation. Dresner and associates[4] reported lacrimal sac and canalicular inflammation caused by retained silicone material.

Silicone intubation is the procedure of choice for stenting a canalicular laceration or area of canalicular stenosis.[1] If a Veirs rod is used and is not present on follow-up examination, however, appropriate radiologic studies should be obtained to rule out retention of the rod within the lacrimal system. Retention of stent material should also be considered in patients with canaliculitis and a history of multiple lacrimal procedures involving stents.

References

1. Jordan, D. R., Nerad, J. A., and Tse, D. T.: The pigtail probe, revisited. Ophthalmology 97:512, 1990.

2. Mensher, J. H., and Leibsohn, J. M.: Accidental ingestion of a Veirs rod. J. Pediatr. Ophthalmol. Strabismus 16:194, 1979.

3. Rootman, D. S., Insler, M. S., and Wolfley, D. E.: Canaliculitis caused by *Mycobacterium chelonae* after lacrimal intubation with silicone tubes. Can. J. Ophthalmol. 24:221, 1989.

4. Dresner, S. C., Codere, F., Brownstein, S., and Jouve, P.: Lacrimal drainage system inflammatory masses from retained silicone tubing. Am. J. Ophthalmol. 98:609, 1984.

5. Yeatts, R. P., and Crum, B.: An unusual complication of nasolacrimal duct probing. Ophthalmic Surg. 20:490, 1989.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Successful Treatment of Recurrent Corneal Erosion With Nd:YAG Anterior Stromal Puncture

EDITOR:

In the article, "Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal puncture," by H. S. Geggel (Am. J. Ophthalmol. 110:404, October 1990), the author used laser technology to address some concerns regarding the stromal puncture procedure as it was originally introduced.[1] These include corneal scarring, depth and reproducibility of penetration, and the potential for corneal perforation. We believe his concerns are reasonable and applaud his efforts to address them. However, a simpler, less expensive technology involving conventional surgical instruments may adequately resolve these concerns.

The most critical concern, that of potential corneal perforation, can be minimized by the use of a large-bore (20-g) needle[2] or eliminated by the use of a standardized specially designed needle (LOOK, Inc., Norwell, Massachusetts), which is incapable of deep corneal penetration.[3]

Another concern, depth and reproducibility of corneal penetration, has also been addressed without laser technology. Human cadaver eye studies have demonstrated that this specially designed small-bore (25-g) needle produces consistent, fine, shallow corneal penetrations, even with purposely inconsistent manual pressure. These penetrations measured 15 to 250 μm (mean, 108 μm). Penetrations of 55 to 415 μm (mean, 208 μm) were produced in the same study with a straight fine-gauge needle[3] (Figs. 1 and 2). Additionally, histologic studies performed by Dr. MacRae have shown that YAG puncture sites disrupt more epithelium and have less predictable penetration than needle puncture[2]; however, these laser punctures were performed without débridement, which Dr. Geggel advocates in his article.

A related issue is the degree of corneal scarring. No patient has been described to have lost a line of visual acuity from stromal puncture over the visual axis,[2] and neither objective measurements nor subjective questioning of ten patients in one study who had undergone micropuncture within the visual axis disclosed any glare problems.[3] Large triangular corneal scars as described by Dr. Geggel have not been observed with the fine-gauge, specially designed needle, and we have been impressed with how well any corneal puncture scars fade with time. We have also been pleased with how well patients generally tolerate the stromal puncture procedure. Two angulations in the shaft of the standardized needle keep the needle tip out of the patient's view during the procedure, thus minimizing anxiety and the risk of head jerk reactions.

The YAG stromal puncture procedure as described by Dr. Geggel requires epithelial débridement of the entire area to be treated. It is unclear how this differs from superficial epithelial keratectomy, which is also an effective treatment for recurrent erosion.[4] One might question whether YAG micropuncture is even needed after epithelial débridement. One of the advantages of mechanical micropuncture is that the puncture sites can usually be applied through corneal epithelium,[1-3] thereby minimizing both healing time and patient discomfort.

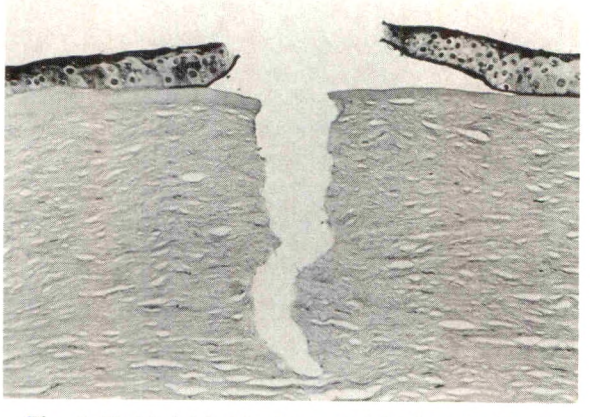


Fig. 1 (Rubinfeld, MacRae, and Laibson). Human cadaver eye after stromal puncture with straight needle (hematoxylin and eosin, × 50).

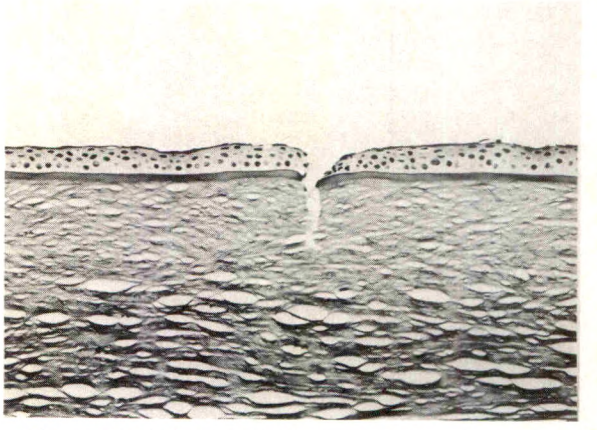


Fig. 2 (Rubinfeld, MacRae, and Laibson). Human cadaver eye after stromal puncture with specially designed needle (hematoxylin and eosin, × 50).

A final point relates to cost, accessibility, and convenience. We believe that a readily available mechanical instrument costing $6.00 provides excellent, reliable, consistent, cost-effective surgical results. Although the medical use of lasers is associated with a certain aura of excitement, in today's climate of cost containment, its use can only be justified if it truly delivers improved clinical results.[5]

ROY S. RUBINFELD, M.D.
Washington, D.C.
SCOTT M. MACRAE, M.D.
Portland, Oregon
PETER R. LAIBSON, M.D.
Philadelphia, Pennsylvania

References

1. McLean, E. N., MacRae, S. M., and Rich, L. F.: Recurrent erosion. Treatment by anterior stromal puncture. Ophthalmology 93:784, 1986.

2. McLean, E. N.: Update on stromal puncture technique. Ophthalmology 97:1245, 1990.
3. Rubinfeld, R. S., Laibson, P. R., Cohen, E. J., Arentsen, J. J., and Eagle, R. C.: Anterior stromal puncture for recurrent erosion. Further experience and new instrumentation. Ophthalmic Surg. 21:318, 1990.
4. Buxton, J. N., and Fox, M. L.: Superficial epithelial keratectomy in the treatment of epithelial basement membrane dystrophy. Arch. Ophthalmol. 101:392, 1983.
5. Anderson, R. L.: Laser madness in medicine. Ophthalmic Surg. 21:539, 1990.

Reply

EDITOR:

Drs. Rubinfeld, MacRae, and Laibson raise several important points regarding the recently described laser stromal puncture technique. To give a proper sequential publication perspective, the original article of Rubinfeld and associates[1] was published after the submission of my article to THE JOURNAL, and the update by McLean[2] was published after my article had already been printed. I did include the article of Rubinfeld and associates in my bibliography in the requested revision.

Which technique is better? McLean believes that a 20-g needle is superior to any other, and Rubinfeld and associates believe that their specially designed 25-g needle is the instrument of choice. Corneal perforation is not a real concern with either of their needles or the Nd:YAG laser. Reproducibility will differ with the different instruments. Rubinfeld and associates acknowledge that the depth of corneal penetration with their needle will vary by a factor of 17 (15 to 250 μm, up to almost one-half corneal thickness). A straight 20-g needle may puncture the cornea at different angles, which creates larger triangular corneal scars.[3] The Nd:YAG laser creates consistent stromal breaks in the range of 10 μm at energy levels between 1.5 and 2.0 mJ after epithelial débridement.[4,5]

I cannot make any comment regarding Dr. MacRae's recent personal observations with the laser treatment performed without epithelial débridement. As stated in the article, I believe débridement is necessary to eliminate the swollen or irregular epithelial surface so that the laser beam can be more critically focused slightly anterior to the basement membrane zone. Figure 4 in my article dramatically contrasts the amount of corneal scarring produced with a bent 25-g needle and the Nd:YAG laser. Corneal scarring will be less with the laser technique or the needle of Rubinfeld and associates. I have not used their instrument and therefore cannot make any direct comparisons. Few studies have really addressed the measurement of glare and contrast sensitivity after stromal puncture, and it is encouraging that some patients of Rubinfeld and associates have not had glare symptoms. As stated in my article, breaks in but not through Bowman's layer can be achieved with the Nd:YAG laser, and this may allow improved adhesion of the basal epithelial cells without corneal scarring.

The question was raised as to whether Nd:YAG micropuncture was needed after epithelial débridement. As stated in the article, the patients in Cases 1 and 2 already had three separate unsuccessful débridements, and the patient in Case 3 had one unsuccessful epithelial débridement before referral. The patients tolerated both needle puncture and laser procedures well. The treated areas were reepithelialized within one to two days and, in my experience, had no more discomfort than patients treated with needle puncture.

I also am cost conscious and applaud all attempts to keep medical costs down. As Drs. Rubinfeld, MacRae, and Laibson know, the true cost of the stromal puncture technique will be the physician procedure fee. Since I have a Nd:YAG laser available in my office, it is accessible and convenient to use. The patient is charged the same fee for stromal puncture whether I use the laser or needle. I do not add an instrument user fee. Other physicians may not have this modality as easily available. I do agree that any needle will be more cost effective and available on a worldwide basis. After the original animal studies were completed in 1988 and early human trials conducted, it was apparent that the laser technique did indeed produce dramatically less corneal scarring than a straight or bent 20- to 26-g needle. I congratulate Dr. Rubinfeld and associates for designing an improved needle and bringing it to the attention of the ophthalmic community.

HARRY S. GEGGEL, M.D.
Seattle, Washington

References

1. Rubinfeld, R. S., Laibson, P. R., Cohen, E. J., Arentsen, J. J., and Eagle, R. C.: Anterior stromal puncture for recurrent erosion. Further experience and new instrumentation. Ophthalmic Surg. 21:318, 1990.
2. McLean, E. N.: Update on stromal puncture technique. Ophthalmology 97:1245, 1990.
3. McLean, E. N., MacRae, S. M., and Rich, L. F.: Recurrent erosion. Treatment by anterior stromal puncture. Ophthalmology 93:784, 1986.
4. Geggel, H. S.: Recurrent corneal erosion. Animal model using Nd:YAG laser as a possible new treatment modality. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 195.
5. Geggel, H. S., and Maza, C. E.: Anterior stromal puncture using the neodymium:YAG laser. Invest. Ophthalmol. Vis. Sci. 31:1555, 1990.

Rapidly Progressive Outer Retinal Necrosis in the Acquired Immunodeficiency Syndrome

EDITOR:

We recently treated an immunosuppressed patient with a distinctive form of acute retinal necrosis that closely resembled the patients described in the article, "Rapidly progressive outer retinal necrosis in the acquired immunodeficiency syndrome," by D. J. Forster, P. U. Dugel, G. T. Frangieh, P. E. Liggett, and N. A. Rao (Am. J. Ophthalmol. 110:341, October 1990). Our patient's immunosuppression was secondary to chemotherapy rather than infection with the human immunodeficiency virus.

A 66-year-old woman had an acute decrease in vision in the left eye of several days duration. A modified radical mastectomy for breast carcinoma had been performed four years previously, with a positive lymph node dissection. One year before visual loss, metastases were detected in the bones, lung, and pleura. At the time of manifestation, she was receiving oral chemotherapy in the form of 20 mg of prednisone per day and 100 mg of cyclophosphamide per day.

Best-corrected visual acuity was R.E.: 20/30 and L.E.: 20/200. Slit-lamp examination of the left eye showed severe keratic precipitates, severe cells and flare, and fibrin in the anterior chamber. There were moderate vitreous cells with widespread retinal necrosis involving the nasal, superior, and inferior retina. The retina immediately surrounding the veins was spared (Figure). The right eye was normal.

Testing for HIV antibody was negative. Testing for acute and convalescent sera for antibodies to cytomegalovirus, herpes simplex virus (types 1 and 2), and varicella zoster virus by enzyme-linked immunsorbent assay were positive at levels consistent with previous exposure but not recent infection. Urine culture was positive for cytomegalovirus; however, buffy coat culture was negative.

A diagnosis of acute retinal necrosis was made and treatment with intravenous acyclovir and methylprednisolone was initiated. The cyclophosphamide was discontinued. Despite this, the lesions showed definite progression into the temporal macular area. After five days, the acyclovir was replaced with intravenous ganciclovir. Subsequently, prompt regression of the necrosis occurred, and pigmentary changes in previously affected areas developed. Prophylactic laser photocoagulation was not performed because of the posterior extent of the necrosis.

Six weeks later, a total rhegmatogenous retinal detachment occurred. No active inflammation was present. The retina was successfully reattached by pars plana vitrectomy and gas injection without scleral buckling. With nine



Figure (Duker and Shakin). Nasal retina of the affected left eye showing diffuse retinal necrosis with distinctive zones of retinal sparing surrounding the veins.

months of follow-up, the retina remained attached, although visual acuity was limited to hand motions.

The findings in our patient share many similarities to the findings in the two patients described by Forster and associates, including immunosuppression, unilateral acute retinal necrosis with perivenous retinal sparing, rapid progression, a poor clinical response to acyclovir, and the development of a rhegmatogenous retinal detachment. Our case shows that this perivenous retinal sparing pattern of acute retinal necrosis is not unique to patients with HIV infection but may occur in conjunction with other modes of immunosuppression as well. Of particular interest is our patient's dramatic positive clinical response to intravenous ganciclovir, after failed intravenous acyclovir treatment.

We suggest that in immunosuppressed patients with this distinctive pattern of acute retinal necrosis, the use of ganciclovir should be considered if a poor initial response to acyclovir is encountered. Although we cannot rule out that reversal of immunosuppression played a role, our patient's pattern of response to antiviral therapy provides indirect evidence that the infectious agent in this condition is either cytomegalovirus or an acyclovir-resistant strain of herpes simplex or zoster virus.

JAY S. DUKER, M.D.
Boston, Massachusetts
ERIC P. SHAKIN, M.D.
Philadelphia, Pennsylvania

Reply

EDITOR:

We read with interest the case reported by Drs. Duker and Shakin. It is obvious from their findings that this type of retinitis can occur in patients without the acquired immunodeficiency syndrome who are otherwise immunosuppressed.

The major difference between this patient and the two we described is that, whereas this patient had a pronounced degree of intraocular inflammation, our patients showed minimal or no vitreitis and anterior chamber reaction. The other features of the disease, particularly the perivenous retinal sparing, the rapidly progressive course, and the poor response to intravenous acyclovir, support the idea that this is similar to the retinitis found in our patients. The difference in the degree of intraocular inflammation between this patient and our patients may be caused by a more profound degree of immunocompromise in our patients.

The observation that the disease seemed to respond better to ganciclovir than to acyclovir is an important one. Since our article was published, we have seen three additional patients, all of whom had AIDS, with a similar type of retinitis. Two of these patients were treated with ganciclovir instead of acyclovir, with stabilization of the retinitis for three months and four months, respectively. Neither of these patients developed retinal detachment while taking ganciclovir. Based on these findings, as well as on those of Drs. Duker and Shakin, we agree that the etiologic agent may be cytomegalovirus or an altered strain of herpes simplex or zoster virus and that ganciclovir should be considered early in the treatment of immunocompromised patients with this type of retinitis.

DAVID J. FORSTER, M.D.
PRAVIN U. DUGEL, M.D.
GEORGE T. FRANGIEH, M.D.
PETER E. LIGGETT, M.D.
NARSING A. RAO, M.D.
Los Angeles, California

Successful Medical Management of *Acanthamoeba* Keratitis

EDITOR:

In the article "Successful medical management of *Acanthamoeba* keratitis," by S. T. Berger, B. J. Mondino, R. H. Hoft, P. B. Donzis, G. N. Holland, M. K. Farley, and J. E. Levenson (Am. J. Ophthalmol. 110:395, October 1990), the authors described achieving a medical cure in six of seven patients with *Acanthamoeba* keratitis treated with triple therapy of propamidine isethionate 0.1%, neomycin–polymyxin B–gramicidin, and miconazole nitrate 1%. In 1988, we reported successful treatment of four patients in whom a 1% suspension of clotrimazole was added to the customary use of propamidine isethionate and neomycin.[1] Clotrimazole and miconazole are closely related imidazole antifungal drugs. We chose to use clotrimazole for two reasons:

antimicrobial susceptibility testing performed at the Centers for Disease Control indicated that clotrimazole was substantially more effective than miconazole, and the acidic vehicle in which miconazole is dissolved is irritating to the eye and not well tolerated by patients over long-term treatment. Our first patient was given topical miconazole and found it caused an unacceptable level of discomfort. We have had no problems with the acceptance of a 1% suspension of clotrimazole dissolved in an artificial tear vehicle.

Given the similarity of our studies, we were extremely surprised that our study was not considered by the authors in the discussion of their results. We concur that medical cure of *Acanthamoeba* keratitis should be the rule rather than the exception. We also agree with the authors that the use of an imidazole drug is a valuable component of triple therapy for *Acanthamoeba* keratitis. We continue to believe, however, that topical 1% clotrimazole is the best drug for this purpose.

WILLIAM T. DRIEBE, JR., M.D.
GEORGE A. STERN, M.D.
Gainesville, Florida

Reference

1. Driebe, W. T., Stern, G. A., Epstein, R. J., Visvesvera, G. S., Adi, M., and Komadina, T.: *Acanthamoeba* keratitis. Potential role for topical clotrimazole in combination chemotherapy. Arch. Ophthalmol. 106:1196, 1988.

Reply

EDITOR:

We appreciate the comments of Drs. Driebe and Stern. The use of topical clotrimazole for treatment of *Acanthamoeba* keratitis was mentioned in the article, but we did not include the article by Driebe and associates in our list of references. We apologize for this unfortunate and unintentional oversight of their excellent work.

STEVEN T. BERGER, M.D.
Orlando, Florida
BARTLY J. MONDINO, M.D.
RICHARD H. HOFT, M.D.
Los Angeles, California
MICHAEL K. FARLEY, M.D.
Newport Beach, California

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Radiology of the Eye and Orbit. Modern Neuroradiology, vol. 4. Edited by Thomas H. Newton and Larissa T. Bilaniuk. New York, Raven Press, 1990. 320 pages, index, illustrated. $115

Reviewed by MELVIN G. ALPER
Chevy Chase, Maryland

This text contains the most current description of the various imaging techniques used today in the diagnosis of a variety of ocular and orbital disease processes. Edited by Drs. Newton and Bilaniuk, it is divided into three sections: magnetic resonance imaging, ultrasonography, and computed tomography.

The chapters on magnetic resonance imaging of ocular and orbital anatomy and pathologic conditions provide the best description of this technique yet compiled. The editors have drawn on the broad experience of neuroradiologists from the universities of California at San Francisco, Illinois, and Pennsylvania. As is usual with multiauthored texts, the product is somewhat uneven.

The technical aspects of magnetic resonance imaging are described in an introductory chapter, which is excellent for the neuroradiologist but too basic and technical for the average ophthalmologist.

The chapter on magnetic resonance imaging of ocular anatomy has only two illustrations, both sagittal sections. Inclusion of axial and coronal illustrations of normal anatomy would have added to this chapter. Some of the illustrations of such rare conditions as Norrie's disease, Warburn syndrome, persistent hyperplastic primary vitreous, retinopathy of prematurity, and morning glory anomaly are well described, but the images appear to have been performed on earlier generation instruments. This probably reflects the rarity of these syndromes. The descriptions of retinoblastoma and malignant melanoma are excellent. The teaching value of all illustrations in these two chapters would have been enhanced if the author had included TR/TE values instead of only referring to T_1-weighted and T_2-weighted images in the legends.

The chapters on magnetic resonance imaging of orbital anatomy and pathologic conditions are the best written and illustrated chapters in this text. The TR/TE values have been included in the legends of these illustrations. Scans of T_1-weighted images show the anatomy in exquisite detail. The pulse sequences of T_2-weighted images are varied to bring out the charactristics of many pathologic lesions. The authors demonstrate the advantages of magnetic resonance imaging in the orbit by use of surface coils and thin sections. The location of space-taking masses by T_1-weighted images and the definition of the pathologic conditions by varying the pulse sequences in longer acquisition times demonstrate that magnetic resonance imaging of the orbit has improved to be the equal of computed tomography. The discussion of neurogenic tumors, optic nerve gliomas, and meningiomas, a special interest of mine, is one of the best written and illustrated to be found in any text. Common orbital tumors, such as cavernous hemangiomas, metastases, and lacrimal gland tumors, are well described and illustrated. I was disappointed that fibrous histiocytomas were not discussed. These tumors have become a fairly common orbital tumor with distinct resonant characteristics. I recommend these two chapters as classics for anyone interested in magnetic resonance imaging of the orbit.

In the chapters on orbital ultrasonography, the authors emphasize that cooperation between the ophthalmologist and radiologist is necessary for adequate testing. Most ophthalmologists in the United States, however, perform their own ultrasound studies. With the advent of modern units, a degree of sophistication has been obtained using high-frequency transducers (7.5 to 12.0 MHz), which affords excellent characterization of space-taking lesions in the orbit and is without parallel in defining inflammatory processes. These chapters are well illustrated, and the discussion is excellent.

In the chapter on computed tomography of orbital anatomy, Drs. Unsold and deGroot present their well-known studies correlating anatomy with computed tomographic scans. This is classic work, previously published in a monograph.

The chapter on computed tomography of ocular and orbital abnormalities demonstrates the broad experience of the authors. The clinical

descriptions by Drs. Char and Unsold cover a variety of lesions in the eye and orbit, which have been correlated with elegant computed tomographic scans performed by the latest generation of computed tomography equipment. Multiplanar reformations are advocated by the authors, but most illustrations demonstrate abnormalities only in axial views. Direct coronal scans are not used, but the reformated coronal scans shown are of equal quality to any in my experience.

This last chapter contains an extensive bibliography that cites the classic papers on computed tomographic scanning of the eye and orbit. The bibliographies of the chapters on magnetic resonance imaging of orbital abnormalities and ultrasonography are equally complete.

The printing is well done and easy to read. Illustrations of ultrasonograms, computed tomographic scans, and magnetic resonance images are reproduced clearly and crisply. This textbook is the finest yet produced on medical imaging of the eye and orbit. It should be in the library of anyone interested in imaging of diseases of these structures.

Handbook of Ocular Drug Therapy and Ocular Side Effects of Systemic Drugs. By Deborah Pavan-Langston and Edmund C. Dunkel. Boston, Little, Brown and Company, 1990. 464 pages, index, illustrated. $32.50

Reviewed by Timothy J. Martin
Winston-Salem, North Carolina

The first half of this text concerns drugs and their ocular implications and is organized by type of medication (antiglaucoma, antibiotics, antifungal, antiviral, mydriatics, and the like). The information in this section is listed by topic rather than by manufacturer, which allows for a more general discussion of the class of drugs, together with some details of clinical management. This organization scheme also encourages summary tables that compare doses, indications, and side effects. This part of the text would be particularly useful to physicians who are not ophthalmologists, because it is a quick reference that explains the likely indication for an ophthalmic drug as well as its potential systemic side effects.

The second half of the text simply lists the visual and ocular side effects of systemic medications. The side effects have been divided into categories (anterior segment, posterior segment, visual fields, and the like). The descriptions of the side effects are brief and entirely without references. I am particularly disturbed by the many entries that bring up the possibility of a certain side effect yet cling to deniability with a question mark, for example, "? optic neuritis." I sympathize with the authors' desire to produce a look-up table so that a patient's medications can be quickly screened for a possible contribution to the initial complaint, but this table has fallen short of the mark. The information offered is brief and unsatisfying, and further referral to the literature would be required.

Eye Diseases in Hot Climates, ed. 2. By John Sandford-Smith. Stoneham, Butterworths & Company, 1990. 241 pages, index, illustrated. $34.95

Reviewed by Frank C. Winter
La Jolla, California

Everybody likes this kind of book, not too big yet full of information. The text deals at a practical level with third-world ophthalmology, concentrating on common conditions that cause blindness and can be prevented or cured.

Beginning with an introduction to world blindness, the text has separate chapters on anatomy and physiology, clinical examination, principles of treatment, and the various structures of the eye and adnexa. Interspersed with these are chapters on specific conditions, such as glaucoma and squint, and a number of tropical diseases, such as trachoma, onchocerciasis, and leprosy. There are many black-and-white illustrations, tables, and diagrams and 90 excellent color photographs.

The book is intended for nonophthalmic professionals working in the developing world, but the type of information focusing on tropical diseases makes it helpful for ophthalmologists and nurses who may be visiting those parts of the world.

The author is an experienced international ophthalmologist who is familiar with the limitations surrounding work in the field. His writing is full of insights and suggestions that help to overcome these limitations. For example, "Some sick children (with xerophthalmia and/

or measles) have not developed ulcers but cannot close their eyes properly. The mothers of these children will need to learn how to close the eyelids, and to apply plenty of antibiotic ointment."

The strength of this book is its simplicity and brevity. It is hard to be brief and yet include everything one would like. Occasionally, however, something falls through the cracks of these pages. For example, we are not told that a scalloped pupil is a sign of iritis in the differential diagnosis of red eye. The consensual pupillary reflex is mentioned, but the useful alternate light stimulation test that compares pupillary input between the two eyes is not described. This simple and objective test can be helpful in evaluating a variety of pathologic conditions that may be obscured by opaque media, language impediment, or lack of cooperation.

Thousands of physicians, nurses, and technicians travel each year to hot climates to share their expertise in ophthalmology. I strongly recommend this book to veterans and rookies alike, and when returning, consider leaving this book behind as a valuable gift for those remaining.

Cataract Surgery. Alternative Small-Incision Techniques. Edited by George W. Rozakis. Thorofare, Slack, Inc., 1990. 194 pages, index, illustrated. $95 (videotape included)

Reviewed by H. E. KOLDER
Iowa City, Iowa

This manual and 60-minute videotape offer how-to instructions for cataract extraction through a small incision without phacoemulsification, including a discussion of "phacofracture" and the "phacosandwich." This material stems from Dr. Luther Fry's new ways of efficiently removing even the hardest lens nucleus without the added costs of phacoemulsification, costs measured in duration of surgery and added risk to the eye as well as in dollars.

Various surgeons have developed new tricks and techniques for small-incision cataract surgery and have described them at meetings. This videotape is for ophthalmologists who have not been able to attend the meetings. The videotape is well done and instructive, and the illustrations are well chosen. Even though success rates and complications are not documented in any detail and there is not much information on the effect of the procedure on the corneal endothelium, this manual and videotape will enable a skillful ophthalmologist to learn the technique. This technique in some cases may be superior to large-incision lens nucleus expression and the pocket type of incision used for phacoemulsification.

The Book List

Advances in Cataract Surgery. Edited by Glen C. Cangelosi. Thorofare, Slack, Inc., 1990. Softcover, 239 pages, index, illustrated. $80

Color Atlas of Ophthalmic Surgery. Strabismus. By Kenneth W. Wright. Philadelphia, J. B. Lippincott, 1990. 261 pages, index, illustrated. $125

Cosmetic Blepharoplasty. By Stephen L. Bosniak. New York, Raven Press, 1990. 114 pages, index, illustrated. $95

Laser Surgery of the Posterior Segment. By Steven M. Bloom and Alexander J. Brucker. Philadelphia, J. B. Lippincott, 1990. 341 pages, index, illustrated. $69.95

Ocular Histopathology. A Guide to Differential Diagnosis. By Curtis E. Margo and Hans E. Grossniklaus. Philadelphia, W. B. Saunders, 1991. 340 pages, index, illustrated. $89

Ptosis, ed. 4. By Michael Callahan and Crowell Beard. Birmingham, Aesculapius Publishing Co., 1990. 319 pages, index, illustrated. $125

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

A randomized trial of sorbinil, an aldose reductase inhibitor, in diabetic retinopathy. Sorbinil Retinopathy Trial Research Group*: Arch. Ophthalmol. 108:1234, 1990.

DIABETIC RETINOPATHY, ALDOSE REDUCTASE INHIBITOR, SORBINIL

A total of 497 patients aged 18 to 56 years with insulin-dependent diabetes mellitus for 1 to 15 years were randomly assigned to take oral sorbinil or placebo and followed up for a median of 41 months. The percentage of patients whose retinopathy severity grade at maximum follow-up had worsened by two or more levels was not significantly different between the two treatment groups (28% in the sorbinil group and 32% in the placebo group, $P = .344$). The number of microaneurysms increased at a slightly slower rate in the sorbinil group than in the placebo group, with statistically significant differences at 21 ($P = .046$) and 30 ($P = .039$) months but not at the maximum follow-up ($P = .156$). About 7% of the patients assigned sorbinil developed a hypersensitivity reaction in the first 3 months. On the basis of these results, it is unlikely that sorbinil administered at a dosage of 250 mg daily for 3 years has a clinically important effect on the course of retinopathy in adults with insulin-dependent diabetes of moderate duration. Our data are consistent, however, with a slightly slower progression rate in the microaneurysm count among patients assigned to take sorbinil, a finding of uncertain clinical importance.—Authors' abstract

*Charles Hennekens, M.D., 55 Pond Ave., Brookline, MA 02146.

Plasma prorenin activity and complications in children with insulin-dependent diabetes mellitus. Wilson, D. M.*, and Luetscher, J. A.: N. Engl. J. Med. 323:1101, 1990.

INSULIN-DEPENDENT DIABETES MELLITUS, PRORENIN LEVELS

Renin, secreted into the blood by the juxtaglomerular cells of the kidneys, is derived from a larger precursor known as prorenin. Plasma prorenin activity was measured in 135 children and adolescents with insulin-dependent diabetes mellitus. The mean (± standard error) plasma prorenin level among the 32 patients over the age of 10 years who had uncomplicated diabetes for less than five years was 8.43 ± 0.58 ng of angiotensin per liter per second, as compared with 7.06 ± 0.32 in 37 control subjects of the same age ($P < .05$). In nine other patients older than age 10 years who had retinopathy or overt albuminuria, the mean plasma prorenin activity was 13.09 ± 1.43 ng of angiotensin per liter per second ($P < .0001$). In 34 patients 10 years of age or older with uncomplicated diabetes, three to 13 measurements of plasma prorenin activity were taken during a follow-up period of six to 39 months. Urinary albumin was determined at each visit, and the patients had regular retinal examinations. Only one of the 20 patients who had consistently normal plasma prorenin values developed overt albuminuria or retinopathy. In contrast, one or both of these complications appeared in eight of the 14 patients who had at least one increased prorenin value. Plasma prorenin values were substantially increased in these eight patients at least 18 months before a complication was noted. Increased plasma prorenin activity identifies a group of young patients with insulin-dependent diabetes who are at high risk for retinopathy and nephropathy.—Michael A. Kass

*Department of Pediatrics, Endocrine Division, Room S-322, Stanford Medical Center, Stanford, CA 94305.

Central visual field changes after panretinal photocoagulation in proliferative diabetic retinopathy. Theodossiadis, G. P.*, Boudouri, A., Georgopoulos, G., and Koutsandrea, Ch.: Ophthalmologica 201:71, 1990.

PROLIFERATIVE DIABETIC RETINOPATHY, PANRETINAL PHOTOCOAGULATION, CENTRAL VISUAL FIELD

Panretinal photocoagulation is used widely for the treatment of proliferative diabetic reti-

nopathy. Unfortunately, panretinal photocoagulation causes alterations in the visual field. In this study, 53 eyes of 42 patients were divided into two different treatment regimens for panretinal photocoagulation. In the first group panretinal photocoagulation was performed up to 2 disk diameters from the upper temporal and lower margin of the fovea. In the second group panretinal photocoagulation was performed up to 3 disk diameters from the upper temporal and lower margin of the fovea and up to 1 disk diameter from the nasal margin of the optic disk. Both treatment regimens were equally effective insofar as treatment of proliferative diabetic retinopathy was concerned. The two groups were also similar as far as postoperative visual acuity. In both groups deterioration of the central visual field was detected, with a much greater deterioration in the first group. Retinal sensitivity was greater at 15 degrees and 30 degrees of eccentricity in the second treatment regimen. Thus, it may be possible to treat proliferative diabetic retinopathy effectively with panretinal photocoagulation sparing greater portions of the central retina and the central visual field.—Michael A. Kass

*54, Omirou St., 106 72 Athens, Greece.

Contact lens surface deposits increase the adhesion of *Pseudomonas aeruginosa*. Butrus, S. I., and Klotz, S. A.*: Curr. Eye Res. 9:717, 1990.

SOFT CONTACT LENSES, SURFACE DEPOSITS, *PSEUDOMONAS* SPECIES

The wearing of soft contact lenses, especially extended-wear lenses, is associated with an increased risk of microbial keratitis. *Pseudomonas aeruginosa* is the most common microorganism isolated from contact lens-associated corneal ulcers. Extended-wear contact lenses used by healthy myopic subjects were studied after removal. The deposits on the lens surface were estimated and then the lenses were incubated with high and low inoculums of *Pseudomonas* species. *Pseudomonas aeruginosa* adhered to the surface of extended-wear contact lenses in direct proportion to the number of deposits on the surface of the lenses. More hydrophobic bacteria adhered ten times greater than did bacteria that were relatively hydrophilic ($P < .005$). Treatment of lenses with commercially available enzymes, such as papain and pork pancreatin, as well as treatment with neuraminidase, mannosidase, glucosidase, and alkylcarboxylic acid for as along as 48 hours failed to reduce subsequent bacterial adhesion in both the high and low inoculum experiments. Thus, soft contact lens surface deposits are a major determinant in the adherence of *P. aeruginosa* to the lenses and enzyme cleaning of the lenses does not significantly reduce bacterial adhesion.—Michael A. Kass

*Infectious Diseases Section, Department of Medicine, Overton Brooks Veterans Administration Medical Center, 510 E. Stoner Ave., Shreveport, LA 71101-4295.

Epikeratoplasty technique without suture using human collagen type IV lenticules. Experimental study on monkey. Albinet, P.*, Romanet, J. P., Mouillon, M., Zerdab, I., Gravagna, P., Tayot, J. L., DuPont, D., and Eloy, R.: J. Fr. Ophtalmol. 13:109, 1990.

EPIKERATOPHAKIA, COLLAGEN LENTICULE, SURGICAL TECHNIQUE

Epikeratophakia is a surgical method to modify the corneal surface and the refraction. Most epikeratophakia techniques to date have used sutures to secure the lenticule. The authors undertook studies in primates in which epikeratophakia was performed with human collagen type IV lenticules secured without sutures. In this technique the corneal epithelium was removed and a trephination was performed to a depth of 0.1 mm. The peripheral cornea was split and a flanged lenticule was placed without sutures. The lenticules remained clear and were covered by epithelium in three of the four animals within a week. Additional studies are needed to determine the stability of the lenticules and the long-term refractive changes.—Michael A. Kass

*P. Albinet, Service d 'Ophtalmologie, Hôpital Albert Michalon, BP 217X, 38043 Grenoble Cedex.

Topical timolol decreases plasma high-density lipoprotein cholesterol level. Coleman, A. L.*, Diehl, D. L. C., Jampel, H. D., Bachorik, P. S., and Quigley, H. A.: Arch. Ophthalmol. 108:1260, 1990.

β-ADRENERGIC ANTAGONISTS, PLASMA LIPID LEVEL

β-adrenergic antagonists taken orally adversely alter plasma lipid profiles. This study was designed to determine whether 0.5% topical timolol maleate has a similar effect. Forty volunteers who were not using medications known to alter plasma lipid levels were recruited for an unmasked study in which each subject served as his or her own control. Twelve subjects did not complete the study because of ocular and systemic side effects or extraneous factors. Twenty-eight subjects used topical timolol for an average of 76 days, with two 12-hour fasting plasma specimens obtained at the beginning and end of the period. Mean total cholesterol and low-density lipoprotein cholesterol levels did not change significantly with treatment. Triglyceride values increased 12%; high-density lipoprotein cholesterol levels decreased 9%; and the total cholesterol–high-density lipoprotein cholesterol ratio increased 8%. Higher baseline high-density lipoprotein cholesterol levels were associated with larger reductions in high-density lipoprotein cholesterol levels. Changes in high-density lipoprotein cholesterol levels of this magnitude have been estimated to increase the risk of coronary artery disease by 21%.—Authors' abstract

*Jules Stein Eye Institute, 2-118, 100 Stein Plaza, UCLA, Los Angeles, CA 90024-7004.

Coffee, caffeine, and cardiovascular disease in men. Grobbee, D. E., Rimm, E. B., Giovannucci, E., Colditz, G., Stampfer, M., and Willett, W.*: N. Engl. J. Med. 323:1026, 1990.

COFFEE, CAFFEINE, CARDIOVASCULAR DISEASE

Many investigators have suspected an association between coffee consumption and coronary heart disease and other cardiovascular diseases. The study sample consisted of 45,589 men in the United States who were 40 to 75 years of age in 1986 and had no history of cardiovascular disease. During two years of follow-up observation, 221 participants had a nonfatal myocardial infarction or died of coronary artery disease, 136 underwent coronary artery surgery or angioplasty, and 54 had a stroke. Total coffee consumption was not associated with an increased risk of coronary heart disease or stroke. The age-adjusted relative risk for all cardiovascular diseases among participants who drank four or more cups of coffee per day was 1.04 (95% confidence interval, 0.74 to 1.46). Increasing levels of consumption of caffeinated coffee were not associated with higher risks of cardiovascular disease. Increased consumption of decaffeinated coffee, however, was associated with a marginally significant increase in the risk of coronary heart disease (relative risk, 1.63; 95% confidence interval, 1.02 to 2.60). There was no pattern of increased risk across the subgroups of participants with increasing intake of caffeine from all sources. Adjustment for major cardiovascular risk factors, dietary intake of fats, and cholesterol intake did not materially alter these associations. This study does not support the hypothesis that coffee or caffeine consumption increases the risk of coronary heart disease or stroke.—Michael A. Kass

*Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave., Boston, MA 02115.

Cerebrovascular complications of the use of the "crack" form of alkaloidal cocaine. Levine, S. R.*, Brust, J. C. M., Futrell, N., Ho, K.-L., Blake, D., Millikan, C. H., Brass, L. M., Fayad, P., Schultz, L. R., Selwa, J. F., and Welch, K. M. A.: N. Engl. J. Med. 323:699, 1990.

CRACK COCAINE, CEREBROVASCULAR DISEASE

The use of cocaine, especially one of its alkaloidal forms known as crack, has been increasingly associated with cerebrovascular disease. Twenty-eight patients were identified who had a stroke during or within 72 hours of exposure to crack cocaine. Of the 28 patients, 18 had cerebral infarctions, five had subarachnoid hemorrhages, four had intraparenchymal hemorrhages, and one had a primary intraventricular hemorrhage. Eighteen of the 28 patients (64%) had acute neurologic symptoms immediately or within one hour of using cocaine. Fifteen patients (45%) with either occlusive or hemorrhagic strokes had severe headache as an early symptom. Vasculitis was not suggested by radiography in any patient, nor was it identified on pathologic examination in the one patient who died. All of the patients were young (mean

age, 34 years; range, 23 to 49 years) and had no other apparent, direct cause of stroke. Other risk factors for stroke among the patients included mild mitral valve prolapse in four patients, hypertension in four patients, cigarette smoking in eight patients, and regular alcohol use in six patients. Thus, there is a strong temporal association of the use of alkaloidal cocaine (crack) with both ischemic and hemorrhagic cerebrovascular events. A thorough history focusing on the use of cocaine and toxicologic screening of urine and serum should be part of the examination of any young patient with a stroke.—Michael A. Kass

*Center for Stroke Research, Department of Neurology, K-11, Henry Ford Hospital and Health Science Center, 2799 W. Grand Blvd., Detroit, MI 48202-2689.

Prevention of second primary tumors with isotretinoin in squamous-cell carcinoma of the head and neck. Hong, W. K.*, Lippman, S. M., Itri, L. M., Karp, D. D., Lee, J. S., Byers, R. M., Schantz, S. P., Kramer, A. M., Lotan, R., Peters, L. J., Dimery, I. W., Brown, B. W., and Goepfert, H.: N. Engl. J. Med. 323:795, 1990.

CANCER PREVENTION, ISOTRETINOIN

Patients with head and neck cancers who are free of disease after therapy remain at high risk for both recurrent and second primary tumors. Retinoids have proved effective in the treatment of premalignant oral lesions and are promising agents for the prevention of epithelial cancers. The sample consisted of 103 patients who were disease-free after treatment for squamous cell carcinoma of the larynx, pharynx, or oral cavity. After completion of surgery, radiotherapy, or both, these patients were randomly assigned to receive either isotretinoin, 50 to 100 mg/m^2 of body-surface area per day, or placebo for 12 months. The treatment and placebo groups did not differ in the number of local, regional, or distant recurrences of the primary cancers. The isotretinoin group, however, had significantly fewer second primary tumors. After a median follow-up of 32 months, two patients (4%) in the isotretinoin group had second primary tumors, as compared with 12 (24%) in the placebo group ($P = .005$). Multiple second primary tumors occurred in four patients, all of whom were in the placebo group. Thus, it appears that daily treatment with high doses of isotretinoin is effective in preventing second primary tumors in patients who have been treated for squamous cell carcinoma of the head and neck, although this treatment does not prevent recurrences of the original tumor.—Michael A. Kass

*Department of Medical Oncology, Box 80, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.

Cell proliferation in carcinogenesis. Cohen, S. M., and Ellwein, L. B.: Science 249:1007, 1990.

CANCER INDUCTION, CELL PROLIFERATION, NONGENOTOXIC COMPOUNDS

Chemicals that induce cancer at high doses in animal bioassays often fail to fit the traditional characterization of genotoxins. Many of these nongenotoxic compounds (such as sodium saccharin) have in common the property that they increase cell proliferation in the target organ. A biologically based, computerized description of carcinogenesis was used to show that the increase in cell proliferation can account for the carcinogenicity of nongenotoxic compounds. The carcinogenic dose-response relationship for genotoxic chemicals (such as 2-acetylaminofluorene) was also due in part to increased cell proliferation. Mechanistic information is required for determination of the existence of a threshold for the proliferative (and carcinogenic) response of nongenotoxic chemicals and the estimation of risk for human exposure.—Authors' abstract

Induction of donor-specific unresponsiveness by intrathymic islet transplantation. Posselt, A. M., Barker, C. F., Tomaszewski, J. E., Markmann, J. F., Choti, M. A., and Naji, A.*: Science 249:1293, 1990.

PANCREATIC ISLET TRANSPLANTATION, DIABETES MELLITUS, THYMUS GLAND

The application of isolated pancreatic islet transplantation for treatment of diabetes mellitus has been hampered by the vulnerability of islet allografts to immunologic rejection. Rat islet allografts that were transplanted into the thymus of recipients treated with a single injec-

tion of anti-lymphocyte serum survived indefinitely. A state of donor-specific unresponsiveness was achieved that permitted survival of a second donor strain islet allograft transplanted to an extrathymic site. Maturation of T cell precursors in a thymic microenvironment that is harboring foreign alloantigen may induce the selective unresponsiveness. This model provides an approach for pancreatic islet transplantation and a potential strategy for specific modification of the peripheral immune repertoire.—Authors' abstract

*Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA 19104.

Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. I. Physical Health. Wolfe, W. H.*, Michalek, J. E., Miner, J. C., Rahe, A., Silva, J., Thomas, W. F., Grubbs, W. D., Lustik, M. B., Karrison, T. G., Roegner, R. H., and Williams, D. E.: JAMA 264:1824, 1990.

HERBICIDES, DIOXIN, VIETNAM VETERANS, PHYSICAL HEALTH

The Air Force Health Study is a 20-year comprehensive assessment of the health of Air Force veterans who were involved in aerial spraying of herbicides in Vietnam. The study compares the health of veterans exposed to herbicides to a comparison group of other Air Force veterans primarily involved in cargo missions in Southeast Asia. Nine hundred ninety-five veterans exposed to herbicides and 1,299 comparison subjects were examined in 1987. Demographic and current socioeconomic characteristics of both groups were similar. The two groups had similar prevalences of reported health problems, skin conditions, hepatic diseases, cardiovascular diseases, and immune profiles. The one area in which veterans exposed to herbicides differed from control subjects was the prevalence of basal cell carcinoma. After adjustment for sun exposure and average residential latitude, the veterans exposed to herbicides had a higher prevalence of basal cell carcinoma (8.3%) than did the comparison subjects (6.2%). Of the 78 veterans exposed to herbicides with basal cell carcinoma, 24 (30.8%) had two or more occurrences of this malignancy as compared to 15 of 76 (19.7%) in the comparison group. The veterans exposed to herbicides and the control group were not different with respect to melanoma and systemic cancer.—Michael A. Kass

*Epidemiology Division, USAF School of Aerospace Medicine (AFSC), Brooks Air Force Base, TX 78235-5301.

Health status of Air Force veterans occupationally exposed to herbicides in Vietnam. II. Mortality. Michalek, J. E., Wolfe, W. H.*, and Miner, J. C.: JAMA 264:1832, 1990.

HERBICIDES, DIOXIN, VIETNAM VETERANS, MORTALITY

This report compares the noncombat mortality of 1,261 veterans exposed to herbicides in Vietnam to that of a comparison population of 19,101 other Air Force veterans primarily involved in cargo missions in Southeast Asia. The indirectly standardized all-cause death rate among veterans exposed to herbicides is 2.5 deaths per 1,000 person-years, the same as that among comparison subjects. After adjustment for age, rank, and occupation, the all-cause standardized mortality ratio was 1.0. In adjusted cause-specific analyses, no significant group differences were found regarding accidental, malignant neoplasm, and circulatory deaths. These data are not supportive of a hypothesis of increased mortality among veterans exposed to herbicides.—Michael A. Kass

*Epidemiology Division, USAF School of Aerospace Medicine (AFSC), Brooks Air Force Base, TX 78235-5301.

The status of women at one academic medical center. Breaking through the glass ceiling. Nickerson, K. G.*, Bennett, N. M., Estes, D., and Shea, S.: JAMA 264:1813, 1990.

ACADEMIC PROMOTION FOR WOMEN

Despite recent gains in admission to medical school and in obtaining junior faculty positions, women remain underrepresented at senior academic ranks and in leadership positions in medicine. This discrepancy has been interpreted as evidence of a "glass ceiling" that prevents all but a few exceptional women from

gaining access to leadership positions. We analyzed data from Columbia University College of Physicians & Surgeons, New York, NY, for all faculty hired from 1969 through 1988 and found that the likelihood of promotion on the tenure track was 0.40 for women and 0.48 for men (ratio, 0.82; 95% confidence interval, 0.56 to 1.20); on the clinical track the likelihood of promotion was 0.75 for women and 0.72 for men (ratio, 1.04; 95% confidence interval, 0.56 to 1.94). Additional analysis of current faculty showed that in the academic year 1988–1989 the proportion of women at each tenure track rank at the College of Physicians & Surgeons equaled or exceeded the national proportion of women graduating from medical school, once allowance was made for the average time lag necessary to attain each rank. On the clinical track women were somewhat overrepresented, particularly at the junior rank. National data that describe medical school faculty, which combine tenure and clinical tracks, showed that in 1988 women were proportionately represented at each rank once the lead time from graduation was considered. We conclude that objective evidence shows that women can succeed and are succeeding in gaining promotions in academic medicine.—Authors' abstract

*Department of Medicine, Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York, NY 10032.

Hematogenous photosensitization. A mechanism for the development of age-related macular degeneration. Gottsch, J. D.*, Pou, S., Bynoe, L. A., and Rosen, G. M.: Invest. Ophthalmol. Vis. Sci. 31:1674, 1990.

AGE-RELATED MACULAR DEGENERATION, PHOTOSENSITIZATION, SUPEROXIDE ANION, SINGLET OXYGEN

Despite numerous investigations, the pathogenesis of age-related macular degeneration remains elusive. The authors offer a theory that age-related macular degeneration develops as a result of photosensitization of the choriocapillaris, Bruch's membrane, and the retinal pigment epithelium by photoactive compounds in the blood. The photoactive compound, protoporphyrin IX, is a naturally occurring precursor molecule of hemoglobin that is found in erythrocytes and plasma, and this compound is capable of generating superoxide anion and singlet oxygen. The amount of reactive-oxygen species produced by this system is dependent on the concentration of protoporphyrin IX and the intensity and wavelength of light. The authors propose that the photogenerated oxidants damage the vascular endothelium of the choriocapillaris, Bruch's membrane, and the retinal pigment epithelium, necessitating a reparative process. Such a reparative process would include features seen in age-related macular degeneration, such as a thickening of Bruch's membrane as well as retinal pigment epithelial atrophy and hyperplasia. It is possible that phototoxic damage could be prevented by enhancing protective enzymes, increasing scavenger substances, or supplying appropriate filters to eliminate the exciting wavelengths of light.—Michael A. Kass

*Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Maumenee Bldg. 305, 600 N. Wolfe St., Baltimore, MD 21205.

Photoreceptor degeneration in inherited retinal dystrophy delayed by basic fibroblast growth factor. Faktorovich, E. G., Steinberg, R. H., Yasumura, D., Matthes, M. T., and LaVail, M. M.*: Nature 347:83, 1990.

RETINAL DEGENERATION, β-FIBROBLAST GROWTH FACTOR

In a variety of inherited retinal degenerations, the photoreceptors degenerate and disappear. In RCS rats the inherited retinal dystrophy appears to be caused by a mutant gene that is expressed in the retinal pigment epithelial cells and leads to loss of the photoreceptor cells. The photoreceptors can be rescued from degeneration by exposure to wild-type retinal pigment epithelial cells in experimental chimaeras or by transplantation of retinal pigment epithelial cells from normal rats. In both cases, the rescue extends beyond the immediate boundaries of the normal retinal pigment epithelial cells, which suggests a trophic action of a diffusible factor or factors from the normal retinal pigment epithelial cells. β-fibroblast growth factor was injected into the subretinal space or the vitreous of RCS rats at postnatal day 23 when photoreceptor degeneration had just begun. One and two months after subretinal injection there was extensive rescue of photoreceptors in the RCS rats. One and two months after intravitreal injection there was

even more widespread rescue that almost covered the entire retina. These findings suggest that β-fibroblast growth factor can act as a survival-promoting neurotrophic factor in a hereditary neuronal degeneration.—Michael A. Kass

*Department of Ophthalmology, University of California at San Francisco, San Francisco, CA 94143-0730.

Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. Taylor, H. R.*, Pacqué, M., Muñoz, B., and Greene, B. M.: Science 250:116, 1990.

ONCHOCERCIASIS, IVERMECTIN

Approximately 85 million people live in areas endemic for onchocerciasis. In some hyperendemic areas more than 50% of the inhabitants will become blind from this disease before their death, and life expectancy of those who are blind is one-third that of their sighted peers. Ivermectin is effective against a wide range of parasites, and this drug may revolutionize the treatment of onchocerciasis. The effect of ivermectin treatment on transmission of onchocerciasis within the community was assessed by determining the incidence of new infection in children. Ivermectin was distributed annually on three occasions to eligible members of a population of approximately 14,000 people living on a rubber plantation in a forest area endemic for onchocerciasis. After two years, the prevalence of infection in 5-year-old children decreased by 21%. The annual incidence in an uninfected cohort of children decreased by 35% and, after age-specific adjustment, the reduction in incidence in 7- to 12-year-old children was 45%. Thus, distribution of ivermectin to a community led to a significant reduction in incidence of new infection. These findings suggest that ivermectin can be important in reducing the transmission of onchocerciasis in populations at risk for the disease.—Michael A. Kass

*Wilmer Ophthalmological Institute, Johns Hopkins University, Baltimore, MD 21205.

Long-term effect of acetazolamide in a patient with retinitis pigmentosa. Chen, J. C., Fitzke, F. W., and Bird, A. C.: Invest. Ophthalmol. Vis. Sci. 31:1914, 1990.

RETINITIS PIGMENTOSA, ACETAZOLAMIDE

In retinitis pigmentosa, central vision is usually preserved until late in the disease unless there is coincident macular edema. Recently, it has been demonstrated that acetazolamide can increase visual acuity in certain patients with macular edema. A 48-year-old woman with autosomal dominant retinitis pigmentosa was treated with 500 mg of acetazolamide per day for three months. During this time, visual acuity improved from hand motions to 20/120 in the right eye and from 20/60 to 20/40 in the left eye. Fluorescein angiography disclosed an improvement in macular edema in the right eye with decreased dye leakage. Automated perimetry showed small to moderate improvement in scotopic retinal function at the four positions closest to fixation in the left eye. Surprisingly, there was also a progressive improvement of more than 2 log units in scotopic sensitivity in the superonasal paracentral visual field over the course of treatment. This improvement extended as far as 30 degrees from fixation and in certain test positions reached as much as 3 log units. The authors hypothesize that the therapeutic effect of acetazolamide is mediated by an alteration of retinal pigment epithelial function restoring disturbed polarity to a more normal state.—Michael A. Kass

*Professiorial Unit, Moorfields Eye Hosptial, City Rd., London EC1V 2PD, England.

Visual disturbances, serum glycine levels and transurethral resection of the prostate. Mizutani, A. R., Parker, J., Katz, J., and Schmidt, J.: J. Urol. 144:697, 1990.

DECREASED VISUAL ACUITY, TRANSURETHRAL RESECTION OF THE PROSTATE, SERUM GLYCINE LEVELS

Transient visual disturbances are common in patients undergoing transurethral resection of the prostate. It has been suggested recently that these visual disturbances are caused by high serum concentrations of glycine from the intravasation of irrigant solutions used during the procedure. Glycine is known to function as a neurotransmitter in the central nervous system

and also in retinal amacrine cells and this compound inhibits the function of retinal ganglion and horizontal cells. Eighteen patients undergoing transurethral resection of the prostate were studied prospectively with measurements of visual acuity, serum electrolytes, glucose, ammonia, and glycine concentrations. Four patients (22%) had significant decreases in visual acuity. These patients had extremely high levels of serum glycine in the few hours immediately after the operation. It is not clear whether there is some threshold level at which glycine affects retinal function, or whether patients who develop blurred vision after transurethral resection of the prostate have impaired metabolism of glycine.—Michael A. Kass

Extrageniculate vision in hemianopic humans. Saccade inhibition by signals in the blind field. Rafal, R.*, Smith, J., Krantz, J., Cohen, A., and Brennan, C.: Science 250:118, 1990.

EXTRAGENICULATE VISION, SACCADE INHIBITION

The functional competence of extrageniculate visual pathways in hemianopic humans was demonstrated by showing that distractor signals in the blind half of the visual field could inhibit saccades toward targets in the intact visual field. This inhibitory effect of unseen distractors in patients occurred only when distractors were presented in the temporal half of the visual field, was specific to oculomotor responses, and did not occur in normal subjects. These results show that a peripheral visual signal activates retinotectal pathways to prime the oculomotor system and that these pathways can mediate orienting behavior in hemianopic humans.—Authors' abstract

*Martinez Veterans Administration Medical Center, 150 Muir Rd., Martinez, CA 94553.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

University of Montreal: Macular Diseases in General Ophthalmology

The University of Montreal: Macular Diseases in General Ophthalmology will be held April 4 and 5, 1991, in Montreal, Canada. For further information, write Entretiens Ophtalmologiques de l'Université de Montréal, 2250 est Boul St-Joseph, Montreal, Quebec, Canada, H2H 1G3; telephone (514) 525-6420 or (514) 525-3888.

Association for Research in Vision and Ophthalmology Annual Meeting:

The Annual Meeting of the Association for Research in Vision and Ophthalmology will be held April 28–May 3, 1991, at Sarasota, Florida. Special symposia on Sunday, April 28, include the following: animal rights extremists and vision research; receptors and signal transductions; myopia, human and animal studies; and clinical research in ocular complications of diabetes mellitus. The annual business meeting will be held May 1 and will be followed by the presentation of awards and lectures. Further information is available from the Association for Research in Vision and Ophthalmology, 9650 Rockville Pike, Suite 1502, Bethesda, MD 20814.

Albert Einstein College of Medicine, Montefiore Medical Center: Fourth Annual Paul Henkind Day Ophthalmology Symposium

On June 7, 1991, the Albert Einstein College of Medicine and Montefiore Medical Center will hold its Fourth Annual Paul Henkind Day Ophthalmology Symposium. The symposium will be located at the New York Helmsley Hotel at 212 E. 42nd St., New York City. For further information, write Danny Flood, Office of Continuing Medical Education, 3301 Bainbridge Ave., Bronx, NY 10467; telephone (212) 920-6674.

The University of Illinois at Chicago: Ninth Annual Clinical Challenges Day

On March 13, 1991, the University of Illinois at Chicago will sponsor the Ninth Annual Clinical Challenges Day. Kenneth I. Resnick will chair the event at the University of Illinois Hospital Eye and Ear Infirmary located at 1855 W. Taylor St., Chicago, IL 60612. For further information, telephone (312) 996-4747.

The Iowa Eye Association: Annual Meeting

The Iowa Eye Association in conjunction with the Department of Ophthalmology, University of Iowa will hold its annual meeting June 6–8, 1991, in Iowa City, Iowa. For further information, write Marlys Bartling, Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242; telephone (319) 356-2780.

Manhattan Eye, Ear and Throat Hospital: Corneal Frontiers 1991—Microsurgical Video Conference

The Manhattan Eye, Ear and Throat Hospital: Corneal Frontiers 1991—Microsurgical Video Conference will be held March 16, 1991. For further information, write Kimberly Corbin, Course Coordinator, Department of Ophthalmology, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761; fax (212) 753-7699.

University of Michigan Medical School: 63rd Annual Ophthalmology Spring Postgraduate Conference: Lasers in Ophthalmology: Applications and New Developments

The Office of Continuing Medical Education of the University of Michigan Medical School will sponsor a conference, "Lasers in Ophthalmology: Applications and New Developments," May 17 and 18, 1991. The conference will be held at the University of Michigan W. K. Kellogg Eye Center in Ann Arbor, Michigan. For further information, write Angela C.

Voeller, Office of Continuing Medical Education, G-1100 Towsley Center, Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; telephone (313) 743-2288.

University of Minnesota: Current Concepts in Pediatric Ophthalmology and Strabismus

The University of Minnesota: Current Concepts in Pediatric Ophthalmology and Strabismus will be held April 15 and 16, 1991, in Minneapolis, Minnesota. For further information, write Becky Noren, Registrar, Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware St. S.E., Minneapolis, MN 55455; telephone (612) 626-7600.

Presbyterian Healthcare System: 13th Annual Dallas Spring Symposium

On April 5 and 6, 1991, the Presbyterian Healthcare System will sponsor the 13th Annual Dallas Spring Symposium at the Fogelson Forum Conference Center located in Presbyterian Hospital, Dallas, Texas. The topic is "Lasers in Ophthalmology." For further information, write Paula M. Hall, Program Coordinator, Office of Continuing Medical Education, Presbyterian Healthcare System, 8160 Walnut Hill Lane, Dallas, TX 75231; telephone (214) 891-2323.

Texas Ophthalmological Association: Annual Educational Symposium

The Texas Ophthalmological Association will hold its Annual Educational Symposium March 8–10, 1991, at the Stouffer Austin Hotel in Austin, Texas. For further information, write Sandy Hirsch, Texas Ophthalmological Association, 1801 North Lamar Blvd., Austin, TX 78701; telephone (512) 477-6704.

Washington National Eye Center: The Anterior Segment—Therapeutic Advances

The Washington National Eye Center and the Department of Ophthalmology of the Washington Hospital Center will sponsor their annual symposium, "The Anterior Segment—Therapeutic Advances," April 12 and 13, 1991, at the Washington Hospital Center. For further information, write Penelope A. Helfgott, WNEC, Suite 6B-13, 110 Irving St. N.W., Washington, DC 20010-2975; telephone (202) 877-6982.

Medical College of Wisconsin: Advanced Vitreoretinal Symposium

The Medical College of Wisconsin: Advanced Vitreoretinal Symposium will be held July 25–27, 1991, in Milwaukee, Wisconsin. For further information, write William F. Mieler, M.D., The Eye Institute, Medical College of Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5544.

The Heed Foundation: Board of Directors

Bradley R. Straatsma, of the Jules Stein Eye Institute, has been elected chairman of the Board of Directors of The Heed Foundation, succeeding Frank W. Newell, of the University of Chicago. Froncie A. Gutman, of the Cleveland Clinic, was elected secretary/treasurer to succeed the late David Shoch of Northwestern University. Steven G. Kramer, of the University of California, San Francisco, was named a director. Lee Jampol, of Northwestern University, and Frank Newell will continue as directors.

The Heed Foundation awards fellowships for postresidency training in ophthalmology.

Personals

Stuart L. Fine

Stuart L. Fine has been named Director of the Scheie Eye Institute in Philadelphia and Professor and Chairman of the Department of Ophthalmology at the University of Pennsylvania School of Medicine. Dr. Fine's Chair is named for William F. Norris and George E. de Schweinitz, the first two chairmen of the Department of Ophthalmology at the university.

Peter J. Savino

Peter Savino was selected by the Society of Heed Fellows as the recipient of the 1990 Heed Award. The Heed Award was presented to Dr. Savino by the chairman of the Heed Ophthalmic Foundation, Dr. Frank Newell, during the annual Society of Heed Fellows luncheon held in conjunction with the American Academy of Ophthalmology meeting in Atlanta, Oct. 29, 1990.

The Heed Award recognized Dr. Savino's contributions in clinical care, education, and research in the field of ophthalmology.

Dr. Savino is clinical professor of ophthalmology at the University of Pennsylvania School of Medicine, Director of Neuro-Ophthalmology at Wills Eye Hospital, and the chairman of the Department of Ophthalmology at Graduate Hospital in Philadelphia.

VOLUME 111

MARCH 15

1991

Acc 28.7.93

AMERICAN JOURNAL OF OPHTHALMOLOGY

Monthly since 1884

• ORIGINAL ARTICLES

Retinal Detachments and Choroidal Colobomas
Hanneken, de Juan, McCuen

Spectroscopy of Uveal Melanomas
De Potter, von Weymarn, Zografos

Asteroid Hyalosis and Systemic Disease
Bergren, Brown, Duker

Hereditary Hemorrhagic Macular Dystrophy
Wu, Pruett, Baldinger, Hirose

Muscle Transposition for Strabismus
Buckley, Townshend

Corneal Nerves in Multiple Endocrine Neoplasia Type 2A
Kinoshita, Tanaka, Ohashi, Ikeda, Takai

Plasma Cell Myeloma
Steuhl, Knorr, Rohrbach, Lisch, Kaiserling, Thiel

Complications of Molteno Implant
Melamed, Cahane, Gutman, Blumenthal

Total and Partial Tenonectomy With Trabeculectomy
Miller, Blasini, Shields, Ho

Therapeutic Ultrasound for Glaucoma Treatment
Silverman, Vogelsang, Rondeau, Coleman

Physical Analysis of Iris Contour
Tiedeman

Relative Pupillary Block
Anderson, Jin, Wright

Iris Pigmentation and Thymoxamine
Diehl, Robin, Wand

Heterochromic Iridocyclitis and Ocular Toxoplasmosis
Schwab

Fibrovascularization of Hydroxyapatite Orbital Implant
Shields, Shields, Eagle, De Potter

• EDITORIAL

In Defense of Animal Research
von Noorden

• LETTERS TO THE JOURNAL

Fibrous band causing strabismus
Spierer, Desatnik, Barishak

Refractive change after strabismus surgery
Reynolds, Nelson, Greenwald

Mean visual acuity
Holladay, Prager

Infectious crystalline keratopathy
Kincaid, Fouraker, Schanzlin

Pseudopemphigoid induced by idoxuridine
Kremer, Rozenbaum, Aviel

Keratoconjunctivitis sicca and Lomotil
Mader, Stulting

Oculocardiac reflex during enucleation
Munden, Carter, Nerad

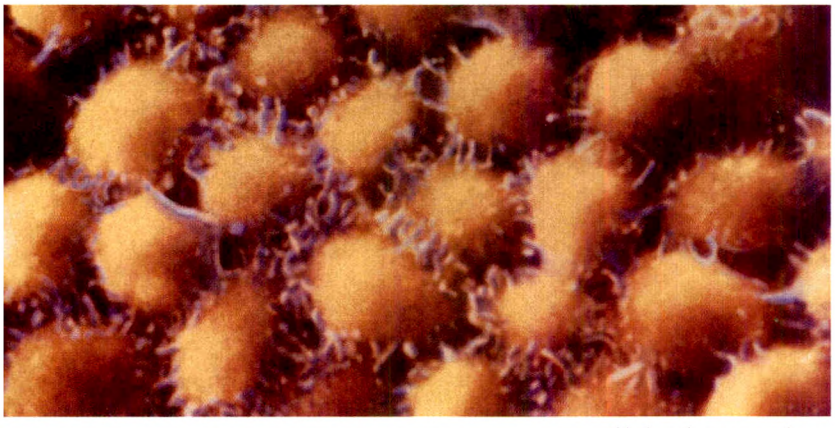
Endophthalmitis and D-arabinitol
Hayasaka, Noda, Setogawa

Unilateral Vogt-Koyanagi-Harada syndrome
Forster, Green, Rao

Corneal curvature and excimer laser ablation
Litwin, Moreira, Ohadi, McDonnell

CALCUTTA CENTRAL LIBRARY UNIVERSITY

AJO®



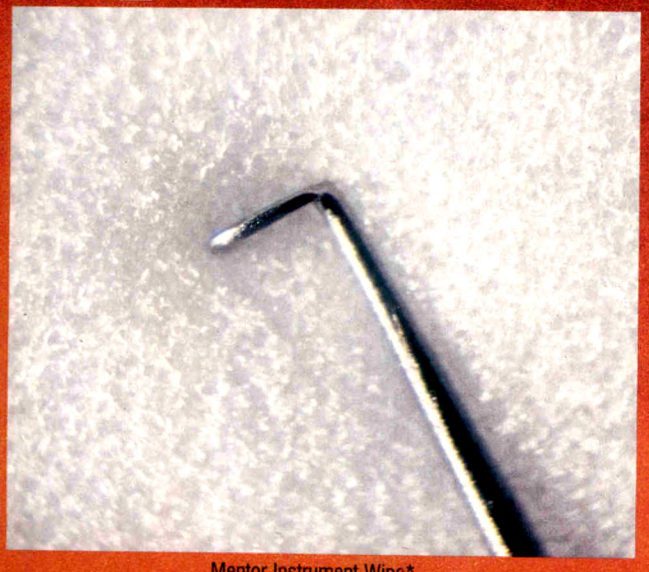
Food for thought

Starving from the lack of a well-balanced perfusion media, these endothelial cells are round and separated at their junctions.* Here, their ability to function as an effective membrane barrier against post-op corneal swelling and cloudiness has been lost.

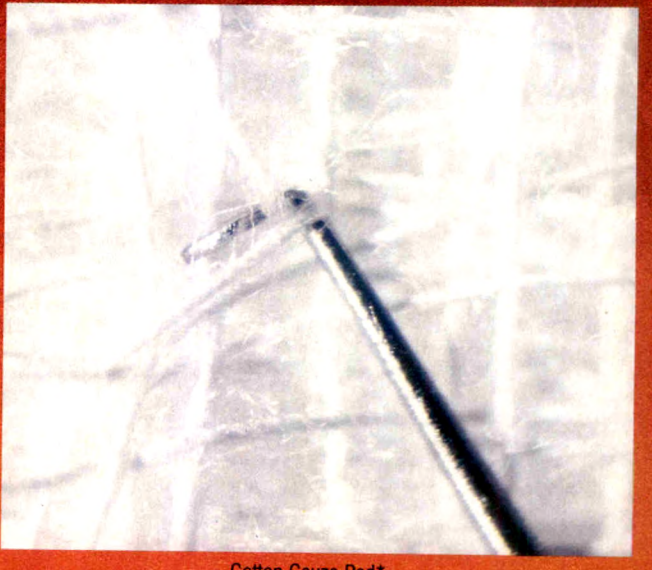
That's why the prospect of a compromised endothelium leaves no room for compromise. Only by feeding endothelial cells a *complete* perfusion diet can the cornea remain true to its fullest potential of clarity and transparency...both during *and* after the surgical procedure. And only BSS PLUS® intraocular irrigating solution contains such a comprehensive formulation of biological foodstuff.

In addition to supplying five essential ions, BSS PLUS® solution nourishes the endothelium with three important constituents—sodium bicarbonate for optimal endothelial pump function and nutrient transport...dextrose, an energy source for cell metabolism and transparent corneas...and glutathione for neutralizing the effects of oxidative stress.

Are your instruments being wiped off...or...wiped out?



Mentor Instrument Wipe*



Cotton Gauze Pad*

The best way to care for and clean your fine microsurgical instruments

Mentor Instrument Wipes

Non snagging - tips won't be inadvertently pulled or bent.

Non linting - the nonwoven PVF material assures a more uniformly clean instrument.

Non abrasive - controlled wetting helps assure sharps and delicate instruments are less likely to be damaged.

Available in a variety of convenient configurations, packaged 20 per box.

NEW



Instrument Wipe - easily and efficiently removes serum and coagulum from delicate instruments.

Instrument Wipe with Pre-cut Eye Drain - aids in removing excess fluid from the surgical area.

Instrument Wipe with Pre-cut Eye Drain and Corneal Light Shield - provides a simple way to block potentially harmful light.

Wipe-X™ Adhesive Backed Instrument Wipe - stays in place on the drape for surgeon access and convenience.

Eye Drain with Collection Bag - introducing a more convenient, effective way to manage excess fluid with the rapid wicking Mentor wipe.

To order or for more information, please write or call:
1-800-992-7557 (toll free in USA) 1-617-871-6950 (MA and outside USA)

*Magnification: 13X

MENTOR O&O INC.

2900 Longwater Drive, Norwell, MA 02061-1612

Mentor® and Wipe-X are trademarks of Mentor O&O, Inc.

Acc 28 1/93

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 March 1991 Series 3, Vol. 111, No. 3

TABLE OF CONTENTS

ORIGINAL ARTICLES

The management of retinal detachments associated with choroidal colobomas by vitreous surgery
Anne Hanneken, Eugene de Juan, Jr., and Brooks W. McCuen II 271

In vivo phosphorus 31 magnetic resonance spectroscopy of human uveal melanomas and other intraocular tumors
Patrick De Potter, Constantin von Weymarn, and Leonidas Zografos 276

Prevalence and association of asteroid hyalosis with systemic diseases
Robert L. Bergren, Gary C. Brown, and Jay S. Duker . 289

Hereditary hemorrhagic macular dystrophy
Gloria Wu, Ronald C. Pruett, John Baldinger, and Tatsuo Hirose 294

A simple transposition procedure for complicated strabismus
Edward G. Buckley and Lois M. Townshend 302

Incidence of prominent corneal nerves in multiple endocrine neoplasia type 2A
Shigeru Kinoshita, Fumi Tanaka, Yuichi Ohashi, Masataka Ikeda, and Shin-ichiro Takai 307

Paraproteinemic corneal deposits in plasma cell myeloma
Klaus-Peter Steuhl, Marcus Knorr, Jens Martin Rohrbach, Walter Lisch, Edwin Kaiserling, and Hans-Jürgen Thiel 312

Postoperative complications after Molteno implant surgery
Shlomo Melamed, Michael Cahane, Isaac Gutman, and Michael Blumenthal 319

A comparison of total and partial tenonectomy with trabeculectomy
Kevin N. Miller, Marino Blasini, M. Bruce Shields, and Chih-Hsiang Ho 323

Therapeutic ultrasound for the treatment of glaucoma
Ronald H. Silverman, Barbara Vogelsang, Mark J. Rondeau, and D. Jackson Coleman 327

A physical analysis of the factors that determine the contour of the iris
James S. Tiedeman 338

The physiologic characteristics of relative pupillary block
Douglas R. Anderson, Jai Chi Jin, and Martha M. Wright 344

The influence of iris pigmentation on the miotic effect of thymoxamine
D. L. Chris Diehl, Alan L. Robin, and Martin Wand . . 351

The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis
Ivan R. Schwab 356

Histopathologic evidence of fibrovascular ingrowth four weeks after placement of the hydroxyapatite orbital implant
Carol L. Shields, Jerry A. Shields, Ralph C. Eagle, Jr., and Patrick De Potter 363

EDITORIAL

In defense of animal research
Gunter K. von Noorden 367

LETTERS TO THE JOURNAL

Aberrant extraocular fibrous band as a cause of strabismus. *Abraham Spierer, Howard Desatnik, and Yomtov Robert Barishak*, **370. Large refractive change after strabismus surgery.** *R. David Reynolds, Leonard B. Nelson, and Mark Greenwald*, **371. Mean visual acuity.** *Jack T. Holladay and Thomas C. Prager*, **372. Infectious crystalline keratopathy after relaxing incisions.** *Marilyn C. Kincaid, Bradley D. Fouraker, and David J. Schanzlin*, **374. Immunofluorescence findings in pseudopemphigoid induced by short-term idoxuridine administration.** *Israel Kremer, Daniel Rozenbaum, and Eliezer Aviel*, **375. Keratoconjunctivitis sicca caused by diphenoxylate hydrochloride with atropine sulfate (Lomotil).** *Thomas H. Mader and R. Doyle Stulting*, **377. The oculocardiac reflex during enucleation.** *Paul M. Munden, Keith D. Carter, and Jeffrey A. Nerad*, **378. Endogenous *Candida* species endophthalmitis associated with increased levels of D-arabinitol in serum and vitreous.** *Seiji Hayasaka, Sachiko Noda, and Tomoichi Setogawa*, **379. Unilateral manifestation of the Vogt-Koyanagi-Harada syndrome in a 7-year-old child.** *David J. Forster, Ronald L. Green, and Narsing A. Rao*, **380. Changes in corneal curvature at different excimer laser ablative depths.** *Kevin L. Litwin, Hamilton Moreira, Camiar Ohadi, and Peter J. McDonnell*, **382.**

CORRESPONDENCE

Anisocoria in the pigmentary dispersion syndrome. *George L. Spaeth*, **384.**

BOOK REVIEWS

Atlas of Ophthalmic Surgery (Norman S. Jaffe). *Reviewed by Mark J. Mannis*, **385. Angle-Closure Glaucoma (Stanley Hyams).** *Reviewed by Howard Perell*, **385. Visual Allusions. Pictures of Perception (Nicholas Wade).** *Reviewed by Peter Thompson*, **386.**

(Table of Contents continued on Advertising Page 8)


Akorn
TOPS THEM ALL
WITH COMPLYING
COLORS
When the American Academy of Ophthalmology requested pharmaceutical manufacturers to provide color-coded caps with all ophthalmic preparations, AKORN responded immediately. That's why AK-Sulf and AK-Pred are available with the tan and pink caps according to the AAO's recommendations. And the rest of AKORN's line of quality, lower cost medications will have color-coded caps in the very near future.
More and more physicians are prescribing AKORN, and the reason is clear. No other company responds faster and gives better service. AKORN. . . our products produce results and reduce costs. That's a promise.
Akorn, Inc.
AK-SULF®
100 Akorn Drive, Abita Springs, LA 70420
AK-PRED®
1-800-535-7155
In Louisiana 1-800-344-2291
FAX 504-893-1257
NASDAQ Symbol: AKRN

AJO® AMERICAN JOURNAL OF OPHTHALMOLOGY®

ISSN 0002-9394 March 1991 Series 3, Vol. 111, No. 3

TABLE OF CONTENTS *(continued from Advertising page 6)*

Clinical Tests of Vision (Lars Frisén). *Reviewed by Michael Wall*, **386. Retinal Nerve Fiber Layer Photography (Louis W. Roloff).** *Reviewed by Nancy Newman*, **387. Lens Implant Power Calculation, ed. 3 (John A. Retzlaff, Donald R. Sanders, and Manus Kraff).** *Reviewed by H. E. Kolder*, **388. Laser Surgery of the Posterior Segment (Steven M. Bloom and Alexander J. Brucker).** *Reviewed by H. Stanley Thompson*, **388. Style. Toward Clarity and Grace (Joseph M. Williams).** *Reviewed by Frank W. Newell*, **389. Advances in Cataract Surgery (Edited by Glen C. Cangelosi), 389. Complications of Glaucoma Therapy (Mark B. Sherwood and George L. Spaeth), 389. Current Concepts of Multifocal Intraocular Lenses (Edited by Andrew Maxwell and Lee T. Nordan), 389. Laser. Its Clinical Uses in Eye Diseases, ed. 2 (Ian J. Constable and Arthur Siew Ming Lim), 390. Les Strabismes. De l'analyse clinique à la synthèse chirurgicale, ed. 2 (Annette Spielmann), 390. The Molecular Biology of the Retina (Edited by Debora B. Farber and Gerald J. Chader), 390. Ophthalmic Echography. Ophthalmic Technical Skills Series (Cynthia J. Kendall), 390. Retinal and Choroidal Manifestations of Systemic Disease (Lawrence J. Singerman and Lee M. Jampol), 390. Small-Incision Cataract Surgery (Edited by James P. Gills and Donald R. Sanders), 390. Textbook of Advanced Phacoemulsification Techniques (Edited by Paul S. Koch and James A. Davison), 390. Visual Fields. Examination and Interpretation (Edited by Thomas J. Walsh), 390.

MEETINGS 391

OBITUARY 394

ABSTRACTS 396

NEWS ITEMS 404

CLASSIFIEDS . . . . . Begins on Advertising 47

COPYRIGHT TRANSFER . . . . . Advertising 11

INSTRUCTIONS TO AUTHORS . . . . . Advertising 27-30

PRODUCTS AND SERVICES . . . . . Begins on Advertising 42

ADVERTISING INDEX . . . . . Advertising 50

PUBLICATION STAFF

MARY L. BORYSEWICZ
Executive Managing Editor

LINDA G. CLAUSEN
Records Manager

KAREN D. JOHNSON
Manuscript Editor

MOLLY MELICK
Assistant to the Editor

DIANN J. MARQUIS
Editorial Assistant

MICHAEL J. LUND
Subscription Correspondent

LYNN ANN LINDVIG
AND
RENEE L. KASTAR
Sales and Production

The Management of Retinal Detachments Associated With Choroidal Colobomas by Vitreous Surgery

Anne Hanneken, M.D., Eugene de Juan, Jr., M.D., and Brooks W. McCuen II, M.D.

We used vitreous surgery to treat seven patients (eight eyes) with complicated retinal detachments associated with choroidal colobomas. All eyes had large choroidal colobomas and no evidence of peripheral retinal breaks. Small, atrophic breaks were detected in five of the eyes and were located in the base of the coloboma in four of the five eyes. Adjunctive surgical techniques were necessary and included cyanoacrylate retinopexy in four eyes, silicone oil tamponade in five eyes, and retinectomy in two eyes. Retinal reattachment was ultimately attained in seven of the eight eyes. The number of surgical procedures ranged from one to five, with an average of three. Postoperative visual acuity of the eyes that underwent anatomically successful procedures ranged from 20/100 to light perception. Proliferative vitreoretinopathy was the most frequent cause of redetachment, occurring in six of the eight eyes.

A CHOROIDAL COLOBOMA is a congenital lesion characterized by the absence of normal retina, retinal pigment epithelium, and choroid. This developmental anomaly is commonly located in the inferonasal region of the fundus and is caused by the failure of closure of the fetal fissure. It is often associated with several other ocular abnormalities, including iris coloboma, loss of inferior lens zonules, cataract, and optic disk abnormalities. The prevalence of retinal detachment in eyes with choroidal colobomas has been reported to be from 23% to 42%.[1,2]

The use of scleral buckling techniques to treat retinal detachments in eyes with choroidal colobomas has resulted in low rates of anatomic success, varying between 35% and 55%.[1,3] Vitreous surgery has been advocated as an alternative to scleral buckling surgery in the treatment of selected retinal detachments in eyes with large chorioretinal colobomas, but there are little data available on its efficacy.[3,4] We used vitreous surgery to treat seven patients (eight eyes) with retinal detachment associated with choroidal coloboma.

Patients and Methods

We reviewed the records of seven consecutive patients (eight eyes) with retinal detachments and posterior colobomas treated by vitrectomy between 1984 and 1990. There were five males and two females, ranging in age from 7 to 42 years. Six of the patients had bilateral retinal detachments. Of these six patients, only one underwent vitreous surgery in both eyes. The remaining five patients had developed phthisis or were not candidates for surgery in their fellow eye. A minimum of six months of follow-up data were available in all patients. The mean follow-up period was 26 months.

All patients had large posterior ocular colobomas associated with iris colobomas, inferior lens opacities, absence of inferior lens zonules, and absence of retinal pigment epithelium and choroid. Patients with peripheral retinal breaks were treated with conventional scleral buckling surgery and were not included in this series. Only eyes with posterior holes or eyes with a rhegmatogenous-appearing retinal detachment in which no holes could be found were considered candidates for vitrectomy. Patients with retinal detachments associated with the morning glory syndrome, isolated optic nerve head coloboma, or optic nerve pit were eliminated

Accepted for publication Nov. 26, 1990.

From the Whittier Institute for Diabetes and Endocrinology, La Jolla, California (Dr. Hanneken); and Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina (Drs. de Juan and McCuen). This study was supported in part by the Adler Foundation, New York, New York (Dr. McCuen). Dr. Hanneken was a 1988–1990 Heed Ophthalmic Fellow.

Reprint requests to Brooks W. McCuen, M.D., Department of Ophthalmology, Duke University Medical Center, Box 3802, Durham, NC 27710.

from this study. Two patients had moderately severe learning disabilities, one patient had a cleft lip and palate, and one patient had a family history of ocular colobomas.

We used a standard three-port vitrectomy procedure. Most patients received general anesthesia. Retrobulbar injections were generally avoided because of the risk of unintentionally penetrating ectatic sclera.

Lensectomies were performed in all eyes using the phacofragmentation unit and a secondary infusion line. After lensectomy, cannulas were placed in the superior quadrants, the contact lens ring was sutured in place, and the axial vitrectomy was performed.

The surgical goals were to release vitreoretinal traction and to identify and seal the retinal breaks. Achieving these goals was challenging in this group of patients. The initial approach involved stripping the cortical vitreous from the retina up to the posterior border of the vitreous base. This was often difficult because of the absence of a complete posterior vitreous detachment and the strong adhesion of the vitreous over regions of detached retina. We attributed the unusually strong vitreoretinal interface to the young age of many of the patients. When peripheral vitreous could not be released adequately or peripheral retinal holes were created, peripheral encircling buckles were placed.

The second surgical objective consisted of identifying the posterior retinal breaks. The retinal breaks were usually small narrow slits in regions of thin rudimentary retina within the colobomatous crater. They were often located in areas beneath a localized posterior vitreous detachment. A useful technique to identify the location of the breaks was to aspirate over regions of rudimentary retina and observe for the presence of schlieren (subtle wavy lines that develop when clear fluids of different viscosities mix).

The third surgical objective was to close and seal the retinal breaks. The atrophic breaks in the base of the coloboma were often treated with cyanoacrylate tissue adhesive. This procedure was performed after a complete fluid-gas exchange. For the adhesive to solidify well, it was necessary to remove all subretinal fluid in the base of the coloboma. This was difficult in cases in which there was a deep pocket of trapped subretinal fluid in the colobomatous crater.

A variety of other procedures were considered helpful adjuncts. Long-acting tamponades with silicone oil, sulfur hexafluoride, or perfluoropropane were always used. Inferior iridectomies were not necessary when silicone oil was used because the patients had inferior iris colobomas. In all patients, a firm chorioretinal adhesion was created at the edge of the coloboma by either endocryotherapy or endolaser photocoagulation. Two rows of treatment were placed along a segment overlapping the edge of the coloboma and the normal retina and choroid in an attempt to isolate the rudimentary retina in the coloboma from the remaining peripheral retina.

Results

The results are summarized in the Table. The retina was successfully reattached in seven of the eight eyes (Figs. 1 and 2). The total number of surgical procedures necessary to achieve retinal reattachment ranged from one to five, with an average of three. Follow-up was available for all patients and ranged from six months to seven years. Postoperative visual acuity in the successfully reattached eyes varied from 20/100 to light perception.

Retinal breaks were identified either preoperatively or intraoperatively in five of the eight eyes. Four of the five breaks were found within the colobomatous crater, in thin rudimentary

TABLE

DATA OF EIGHT EYES WITH RETINAL DETACHMENTS ASSOCIATED WITH CHOROIDAL COLOBOMAS

CASE NO., AGE (YRS)	SURGICAL ADJUNCTS	NO. OF PROCEDURES	RESULTS	VISUAL ACUITY*	FOLLOW-UP (MOS)
1, 42	Silicone	4	Attached	20/400	14
2, 35	Glue	1	Attached	CF	11
3, 24	Silicone, retinectomy	3	Attached	20/100	8
4, 35	Glue	2	Attached	20/200	14
5, 7	Silicone	4	Attached	20/200	84
6, 7	Glue	2	Detached	LP	52
7, 25	Silicone	4	Attached	LP	21
8, 11	Glue, silicone, retinectomy	5	Attached	20/400	6

*CF indicates counting fingers and LP indicates light perception.

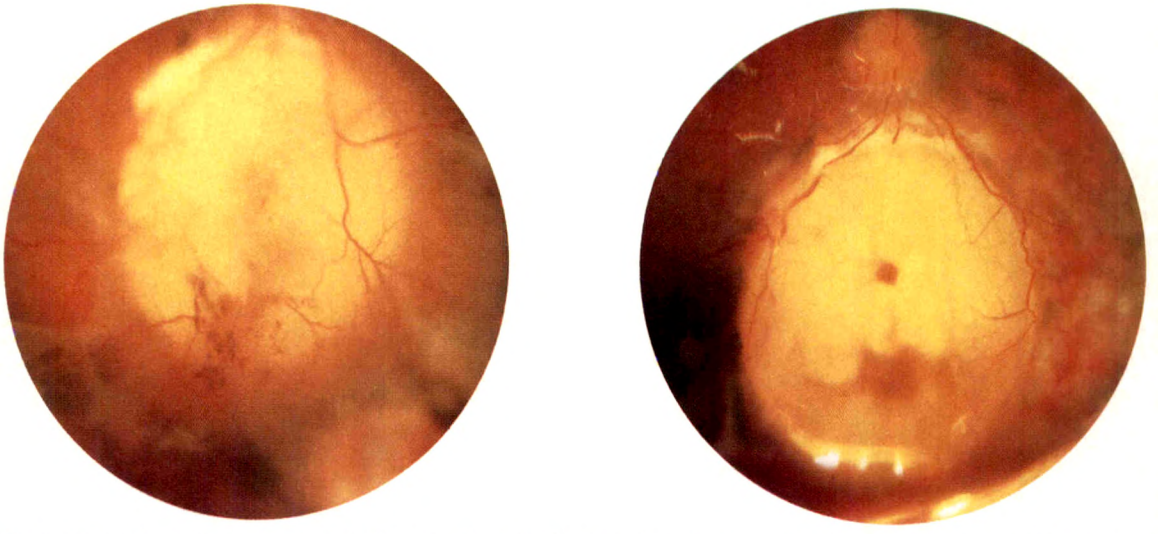


Fig. 1 (Hanneken, de Juan, and McCuen). Case 3. Retinal detachment associated with choroidal coloboma. Left, Fundus of the left eye demonstrating a recurrent retinal detachment with subretinal membranes after initial vitrectomy and fluid-gas exchange. Right, Fundus of the same eye after revision of vitrectomy, retinectomy, removal of subretinal membranes, endocryotherapy, and silicone oil tamponade.

retina. Most patients had only one break in the coloboma, although one patient had two.

Peripheral encircling scleral buckles were present in five of the eight eyes at the final follow-up examination. Two of the patients were initially seen with peripheral buckles already in place, and three patients received scleral buckles during our surgery to support the posterior vitreous base.

Cyanoacrylate retinopexy was used to close and seal the posterior breaks in four of the five eyes in which holes were found. All of the holes treated with glue were closed successfully. In one of the patients, however, the glue did not adhere adequately to the retina and was partially removed (Case 4). This problem was caused by residual subretinal fluid in the base of the coloboma that prevented a tight adhesion between the retina and the glue.

Silicone oil was used in five eyes to achieve a long-term tamponade. In four of the five eyes, the silicone oil was removed after several months. In one of these patients, however, the eye redetached after silicone oil removal, and the silicone oil had to be replaced (Case 8).

The most common postoperative complication was the development of proliferative vitreoretinopathy. Six of the eight eyes developed proliferative vitreoretinopathy, ranging from full-thickness fixed retinal folds in two quadrants to fixed retinal folds of closed funnel shape in four quadrants. Two eyes developed significant tractional subretinal membranes, both of which required removal before the retina could be reattached. Severe anterior vitreous base contraction occurred in another patient and led to the ultimate failure of reattachment surgery (Case 6).

A severe fibrin pupillary membrane occurred postoperatively in one patient (Case 7). This membrane did not resorb with corticosteroid treatment and required surgical removal.

Discussion

In the absence of peripheral retinal breaks, vitreous surgery is the treatment of choice in managing retinal detachment associated with choroidal colobomas. Previously, scleral buckling techniques alone have been used, but the rates of anatomic reattachment have been low.[2,3] In 1983, Gonvers[4] reported the successful use of the silicone oil tamponade to treat one eye with a retinal detachment associated with a choroidal coloboma. Since then, additional reports of retinal detachment caused by chorioretinal colobomas and treated by vitreous surgery have been few.[3]

The relatively poor surgical results in these cases are caused by several key anatomic features that make these eyes uniquely different from other eyes with retinal detachment. One

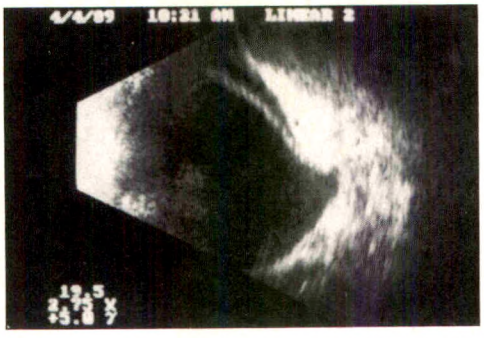


Fig. 2 (Hanneken, de Juan, and McCuen). Case 8. B-scan ultrasound image demonstrating a retinal detachment associated with a large posterior coloboma (horizontal orientation).

of these features is the presence of small slit-shaped retinal breaks in the base of the coloboma. The retinal breaks in these eyes are often difficult to identify both preoperatively and intraoperatively. The retina overlying the coloboma is extremely atrophic, thin, and transparent. The absence of normal retinal pigment epithelium and choroid reduces the contrast and contributes to the problem of visualizing the break. The best intraoperative technique for identifying these breaks within the base of the coloboma is to aspirate fluid above the coloboma and to look for schlieren as subretinal fluid leaks through the retinal break. With this technique, we were able to identify or confirm most of the breaks in our series. However, we were still unable to identify primary retinal breaks in three of our patients.

The absence of a posterior vitreous detachment is another complicating feature in these eyes. Although the typical rhegmatogenous detachment contains a nearly complete posterior vitreous detachment, our cases demonstrated virtually no separation between the cortical vitreous and the retina. The only area where the vitreous was separated from the retina was over the coloboma, where a shallow, partial, posterior vitreous separation was frequently present. This separation was focal, however, and firm vitreoretinal adhesion was present over the remainder of the coloboma and the more peripheral retina.

The absence of a posterior vitreous detachment causes considerable technical difficulty during surgery. This difficulty occurs when attempting to strip firmly attached cortical vitreous from detached retina. We consider it important to separate the posterior vitreous from the retina to reduce the possibility of postoperative vitreous contraction leading to recurrent retinal detachment.

An important consideration in the treatment of this group of patients is the choice and use of chorioretinal adhesive modalities to treat retinal breaks. Traditionally, breaks are treated with thermal irritation of the retinal pigment epithelium and retina to create chorioretinal scarring and adhesion. Within the coloboma, however, the retinal pigment epithelium is abnormal and frequently absent. Laser photocoagulation, cryotherapy, and diathermy do not result in good chorioretinal adhesions within this region. Other alternatives are necessary.

Cyanoacrylate retinopexy[5,6] is a useful technique for closing atrophic breaks in the base of the coloboma. For the adhesive to solidify, the glue must be applied after all residual fluid has been removed from the vitreous cavity by fluid-gas exchange and internal drainage of subretinal fluid. Poor chorioretinal adhesion was encountered in one patient (Case 4) in whom the rudimentary retina within the coloboma could not be completely flattened against the sclera.

Silicone oil was used in five of the eight eyes to achieve a long-term tamponade. It was ultimately removed in four of the five eyes. Because one of these eyes developed a redetachment after the removal of silicone oil, however, we are now more cautious when considering whether to remove it.

Endolaser retinopexy or endocryotherapy is applied along the margin of the coloboma to create a border of chorioretinal adhesion and to separate normal retina from abnormal retina. This treatment was used to limit the extension of potential recurrent subretinal fluid in the base of the coloboma.

The most common cause of retinal redetachment in these cases was proliferative vitreoretinopathy. Seven of the eight eyes in our series redetached, and the detachment in all but one of these eyes was caused by transvitreal, circumferential, or subretinal tractional membranes. Severe anterior vitreous base contraction accounted for the ultimate failure in one patient (Case 6). The reason for the high prevalence of proliferative vitreoretinopathy is not clear, but it may be related to the relatively young age of the patients, the chronicity of the detachments, or the extent of laser or cryotherapy.

Although multiple operations may be necessary, vitreous surgery provides an effective treatment of complicated retinal detachments in patients with choroidal colobomas. The risks

are great in these patients because they are often monocular, the procedure is difficult, and the prevalence of proliferative vitreoretinopathy is high. Fortunately, however, the use of vitreous surgical techniques has improved the anatomic and visual results in these complicated cases.

References

1. Jesberg, D. O., and Schepens, C. L.: Retinal detachment associated with coloboma of the choroid. Arch. Ophthalmol. 65:163, 1961.

2. Patnaik, B., and Kalsi, R.: Retinal detachment with coloboma of the choroid. Indian J. Ophthalmol. 29:345, 1981.

3. Wang, K., and Hilton, G. F.: Retinal detachment associated with coloboma of the choroid. Trans. Am. Ophthalmol. Soc. 83:49, 1985.

4. Gonvers, M.: Temporary use of silicone oil in the treatment of special cases of retinal detachment. Ophthalmologica 187:202, 1983.

5. McCuen, B. W., II, Hida, T., and Sheta, S. M.: Transvitreal cyanoacrylate retinopexy in the management of complicated retinal detachment. Am. J. Ophthalmol. 104:127, 1987.

6. Sheta, S. M., Hida, T., and McCuen, B. W., II: Cyanoacrylate tissue adhesive in the management of recurrent retinal detachment caused by macular hole. Am. J. Ophthalmol. 109:28, 1990.

OPHTHALMIC MINIATURE

There was one point that my father had noted about Lincoln's physiognomy that I have never seen recorded. It was that the left eye, from time to time, looked queer and then suddenly "crossed," i.e., turned up. At the time when my father told me this it did not strike me as having the least importance. Older grown, however, and become an oculist, I was struck one day by the recollection and then by the meaning of the fact itself. Lincoln had been the victim of hyperphoria (a tendency of one eye upward) with, now and then, a momentary hypertropia (actual turning of one eye upward). Such a condition, as all oculists know, gives rise to an intense form of eyestrain and is one of the commonest causes of deep and protracted melancholy—the chronic, inexpressible blues. Here, then, was the probable explanation of the well-known Lincolnian depression of spirits which lasted, off and on, until his death.

Thomas Hall Shastid, *My Father Knew Lincoln*
The Nation 128:227, 1929

In Vivo Phosphorus 31 Magnetic Resonance Spectroscopy of Human Uveal Melanomas and Other Intraocular Tumors

Patrick De Potter, M.D., Constantin von Weymarn, Ph.D., and Leonidas Zografos, M.D.

We studied the feasibility of using the surface coil probe technique for the noninvasive in vivo study of ocular tumors by phosphorus 31 magnetic resonance spectroscopy. The characteristic organophosphate metabolites of suspected uveal melanomas before proton beam irradiation were determined qualitatively by phosphorus 31 magnetic resonance spectroscopy in vivo using a three-turn surface coil. Spectra of choroidal hemangioma, osteoma, and metastasis were also obtained in vivo and compared with those of uveal melanomas. Analysis of spectra performed at 1.5 T showed significant peaks of phosphomonoesters, inorganic phosphate, phosphodiesters, phosphocreatine, and adenosine 5′-triphosphates. The unusually high concentration of phosphodiesters may be considered as a marker for uveal melanomas and other choroidal tumors. By analyzing the ratio of phosphocreatine to phosphodiesters spectral area values, we interpreted qualitatively spectra of intraocular tumors to differentiate malignant tumors from benign lesions. Nevertheless, the main limitation of interpreting the spectra was their contamination by signals from surrounding tissues.

In vivo phosphorus 31 spectroscopy provides a powerful noninvasive method for examining the metabolic processes of cells and tissues. It provides essential biochemical information regarding the principal organophosphates in the cell (state of oxygenation, intracellular pH, and ability to transport various molecules across the cellular membranes).[1] The introduction of the surface coil has enhanced the use of magnetic resonance spectroscopy for the in vivo observation of tumors[2] and the monitoring of ocular tissue metabolites. This has been achieved in animal eyes as well as in human enucleated eyes by studying cornea,[3-5] lens,[6-9] retina,[10] nonocular tumors,[11-20] and ocular tumors.[21-29]

We determined the characteristics of human uveal melanomas and other intraocular tumors by in vivo phosphorus 31 magnetic resonance spectroscopy. By using a surface coil and appropriate radiofrequency pulses, we identified qualitatively and attempted to interpret some markers for uveal melanomas and other choroidal tumors.

Patients and Methods

The magnetic resonance measurements were obtained on ten patients with uveal melanoma and three patients with other intraocular tumors before treatment. Magnetic resonance examinations were also performed on a normal phakic eye and a pseudophakic eye of the same patient to measure the contribution of the lens. Spectra were acquired on a 1.5-T (64-MHz) whole body magnetic resonance system at the Department of Radiology, University Hospital, Zurich, Switzerland.

For the spectroscopy of the eye, we used a balanced-matched[30] three-turn surface coil of 3 cm in diameter that was designed and constructed at the University Hospital of Zurich. The coil, resonating at 25.86 MHz, was used for both excitation and reception of the signal. As an external reference for pulse adjustments and as a reference in the phosphorus 31 magnetic

Accepted for publication Dec. 6, 1990.

From the University Eye Hospital, Lausanne, Switzerland (Drs. De Potter and Zografos), and Department of Radiology, University Hospital, Zurich, Switzerland (Dr. von Weymarn). This study was supported in part by grants from the Scientific Research Foundation, University Eye Hospital, Lausanne, Switzerland, funds from Professor C. Gailloud, and the Schweizerisher Funds zur Bekampfung der Blindheit.

Reprint requests to Leonidas Zografos, M.D., University Eye Hospital, 15 Avenue de France, CH 1004 Lausanne, Switzerland.

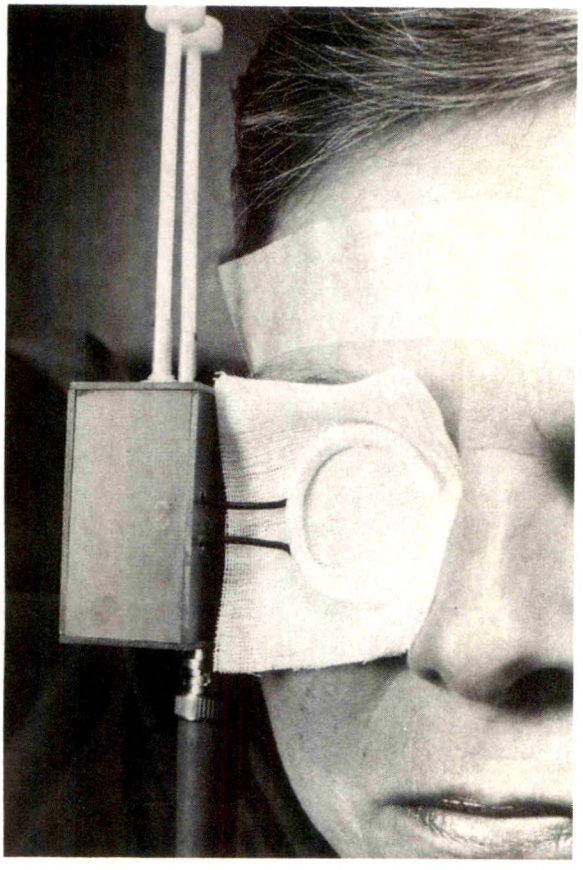


Fig. 1 (De Potter, von Weymarn, and Zografos). The three-turn surface coil of 3 cm in diameter was positioned on the eye containing the tumor with a thin cotton layer between the antenna and the eyelid.

resonance spectrum, we used a small sphere (2 mm in diameter) containing a 1-mol/l solution of hexachlorocyclotriphosphazene, placed in the center of the surface coil. The coil was positioned on the eye with the lesion, with a thin layer of cotton between the eye and the antenna (Fig. 1). We changed the reference volume of the small sphere in two patients (cases 5 and 6), which accounted for the change of amplitude of the reference peak in these spectra. No reference was used in the patients described in Cases 2 and 12. The reference was a control marker that was necessary for power and frequency adjustments when the signal was extremely weak. Quantification with the information data and the reference used was not assessable. Therefore, we analyzed our data qualitatively by comparing peak ratios.

The patients were in a supine position for optimal comfort and immobilization. Each spectrum was obtained in eight-minute intervals, which gave a total examination time of approximately one hour. We performed magnetic resonance spectroscopy of the eye with the tumor and the fellow eye in the same session in only one patient because of the long duration of the procedure. First, a set of transverse images were acquired with the body coil to control the position and the size of the tumor. The subsequent shimming was performed with the surface coil using the proton signal. Shimming was difficult and usually the achievable line width was approximately 30 Hz full width at half maximum. After manual tuning and matching to the phosphorus frequency, the spectra were acquired with a sample frequency of 3,000 Hz, 1,024 data points, and 64 scans with a repetition time of four seconds using an adiabatic radiofrequency pulse for the excitation of the spins.

The pulse length of the adiabatic pulse was adjusted to cover the region of the choroidal tumor. The sensitivity was increased to a depth equal to the diameter of the coil. By experimentally determining portions of equivalent field strength, we found a penetration depth of the pulse to cover one diameter of the coil (Fig. 2). To analyze the spectra, the free induction decay was multiplied with an exponential filter to improve the signal-to-noise ratio. We broadened the lines by approximately 10 Hz, which resulted in an optimal spectral resolution of 22

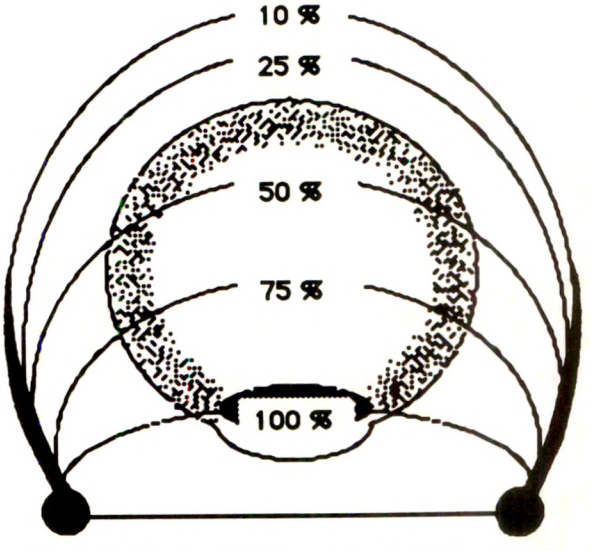


Fig. 2 (De Potter, von Weymarn, and Zografos). The penetration depth of the exciting adiabatic pulse was measured experimentally. The eye is confined within the penetration range of the pulse power. The 10% field represents limits of the coil sensitivity for excitation.

Hz. A convolution-difference filter of 200 Hz was applied to suppress the broad signal of the solid bone. Thereafter, the free induction decay was Fourrier-transformed and phase-corrected. From these spectra, the zero- and first-order phase corrections, the peak positions, peak heights, and peak widths were estimated and input into a least mean square fit program, where the estimated data were fitted to the measured free induction decay. To quantify the analysis, the fitted spectrum was subtracted from the measured one and checked for its performance. The difference between the measured and the fitted data was smaller or equal to 1.5 times the noise level.

Control eyes—The first magnetic resonance measurements were performed on a 35-year-old woman with a phakic left eye and a pseudophakic right eye. A cataract developed after penetrating trauma in the right eye. Extracapsular cataract extraction and insertion of a multifocal intraocular lens were performed one month before the spectroscopy. The left eye had no lens opacities.

Eyes with uveal melanoma—Clinical data regarding the ten patients with uveal melanoma are shown in Table 1. There were five men and five women, who ranged in age from 35 to 72 years. The mean age was 56.1 years. The largest diameter of the tumors varied from 13 to 23 mm (mean, 16.4 mm). The smallest diameter varied from 11 to 21 mm (mean, 15 mm). The height of the tumors varied from 2.5 to 13.2 mm (mean, 7.7 mm). The anterior margin of the tumor was located posterior to the equator in four eyes and anterior to the equator in six eyes. Serous retinal detachment around the tumor was noted in two eyes and a bullous retinal detachment in four eyes. Posterior subcapsular cataract was present in one eye.

The diagnosis of uveal melanoma was established by indirect binocular ophthalmoscopy and real time B-scan ultrasonography. Fundus photography was performed in all patients. Fluorescein angiography and standardized A-scan ultrasonography were performed in all patients. Preoperative transillumination was performed in eight patients before and in two patients after magnetic resonance spectroscopy. The tumor in all eyes provided a circumscribed dark shadow. No extrascleral extension was seen. Tantalum rings were sutured on the sclera around the tumor base to be used as reference markers for alignment of the tumor with the proton beam. Four tantalum rings were sutured on the sclera of five patients, and five rings were sutured on the sclera of three patients.

To decrease the tumor exudation, additional xenon photocoagulation of the tumor surface or around the tumor base was performed in four eyes before magnetic resonance spectroscopy. One eye was enucleated three days after the spectroscopy. Half of the globe of this eye was

TABLE 1
PATIENTS WITH UVEAL MELANOMA STUDIED BY IN VIVO PHOSPHORUS 31 MAGNETIC RESONANCE SPECTROSCOPY

CASE NO., AGE (YRS), SEX	LOCATION OF TUMOR	RETINAL DETACHMENT	TUMOR SIZE (MM)	VOLUME (ML)	PHOTOCOAGULATION	TANTALUM RINGS
1, 41, M	R.E., anterior to equator	Bullous	16 × 14 × 13.2	1.42	No	Yes
2, 68, M	R.E., ciliary body, cataract	No	19 × 17 × 11.4	1.97	No	Yes
3, 56, F	L.E., anterior to equator	No	13 × 13 × 5.1	0.46	Yes	Yes
4, 61, F	R.E., posterior pole	Localized	15 × 14 × 7.3	0.58	Yes	Yes
5, 67, F	R.E., posterior pole recurrence	No	15 × 14 × 5.2	0.50	Yes	Yes
6, 42, M	R.E., posterior pole	No	14 × 11 × 2.5	0.21	Yes	Yes
7, 62, F	R.E., posterior pole	Bullous	19 × 17 × 5.5	0.79	No	No
8, 57, M	L.E., anterior to equator	Bullous	23 × 17 × 8.2	1.54	No	Yes
9, 35, F	R.E., ciliary body	Bullous	23 × 21 × 10	2.11	No	Yes
10, 72, M	R.E., ciliary body	Localized	13 × 12 × 9	0.60	No	No

TABLE 2
PATIENTS WITH OTHER INTRAOCULAR TUMORS STUDIED BY IN VIVO PHOSPHORUS 31 MAGNETIC RESONANCE SPECTROSCOPY

CASE NO., AGE (YRS), SEX	LOCATION AND TYPE OF TUMOR	RETINAL DETACHMENT	TUMOR SIZE (MM)	VOLUME (ML)
11, 60, F	R.E., choroidal metastasis of breast carcinoma, posterior pole	Bullous	20 × 10 × 2	0.36
12, 64, F	R.E., choroidal hemangioma, posterior pole	Bullous	13 × 11 × 3.2	0.27
13, 65, M	L.E., choroidal osteoma	No	10 × 7 × 2	0.15

fixed in a mixture of formaldehyde 4% and glutaraldehyde 1%, dehydrated, and embedded in paraffin. Histologic examination was performed.

Eyes with other intraocular tumors—Clinical data regarding patients with other intraocular tumors are shown in Table 2. A 60-year-old woman was referred for conservative treatment with external beam irradiation of choroidal metastasis in the right eye. She had been treated seven years previously for a breast carcinoma with mastectomy and radiotherapy. The diagnosis of metastatic choroidal tumor was confirmed by clinical examination, fluorescein angiography, and ultrasonography. The volume of the tumor was estimated to be 0.36 ml. Magnetic resonance spectroscopy was performed before the external beam irradiation.

A 64-year-old woman with a juxtapapillary choroidal hemangioma of 0.27-ml volume was examined by spectroscopy before treatment with proton beam irradiation.

A 65-year-old man with a choroidal osteoma located at the posterior pole of the left eye without serous retinal detachment and retinal or vitreous hemorrhage was examined by magnetic resonance spectroscopy. The diagnosis was confirmed by ultrasonography and computed tomography. Measurements showed a tumor with a volume of approximately 0.15 ml.

Peak positions in Table 3 were referenced internally to phosphocreatine. Peak assignments were made by comparison with reported chemical shift data and perchloric acid extracts of cultured human cells.[25]

Results

The main resonance peaks observed in the normal phakic and pseudophakic eye were obtained with a pulse width of one third of the normal pulse power. Spectra were dominated by the phosphate metabolites of the cornea, iris, lens, and extraocular muscles in the eyelid: the external reference; the sugar phosphates band including overlapping resonances from the phosphorylated sugars and the phosphomonoesters caused by the resolution of spectra; phosphorylethanolamine and phosphorylcholine; the inorganic phosphate; the phosphodiesters band, including principally glycerol 3-phosphorylcholine; the phosphocreatine; and the nucleosides triphosphates with the ionized α, β, γ chain-terminal phosphate (Fig. 3, top). In the pseudophakic eye, we noted a general decrease of the baseline spectrum, but the spectrum appears the same in terms of the peaks that are present (Fig. 3, bottom).

In the phakic eye, we calculated the contribution from the lens in the phosphomonoesters (sugar phosphates band), and adenosine triphosphates signals by the ratio of these peaks in pseudophakic and phakic eyes, estimating that contamination from surrounding tissues

TABLE 3
PEAK ASSIGNMENTS FOR IN VIVO PHOSPHORUS 31 MAGNETIC RESONANCE SPECTRA OF EYES WITH TUMORS

CHEMICAL SHIFT (PPM)	PEAK ASSIGNMENT
6.54	Sugar phosphates band (phosphorylated sugars and phosphomonoesters)
5.00	Inorganic phosphate
2.29	Phosphodiesters
0.00	Phosphocreatine
− 2.35	γ-adenosine 5-triphosphate
− 7.72	α-adenosine 5-triphosphate
−16.40	β-adenosine 5-triphosphate

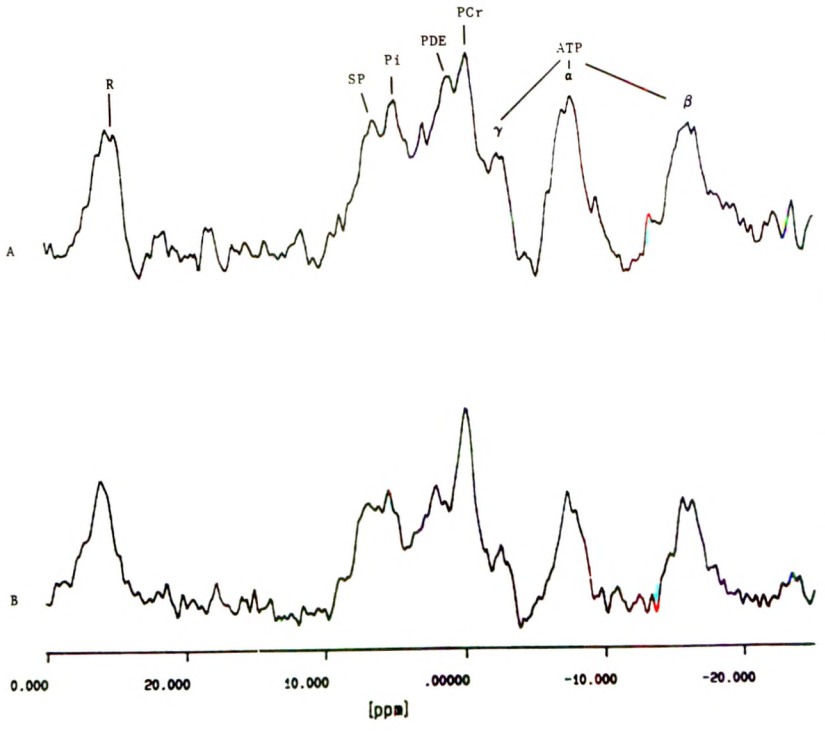


Fig. 3 (De Potter, von Weymarn, and Zografos). In vivo phosphorus 31 magnetic resonance spectrum of a normal phakic eye (top) and a pseudophakic eye (bottom) obtained with radiofrequency pulse width of one third of the normal pulse power. R, external reference; SP, sugar phosphates (phosphorylated sugars and phosphomonoesters); Pi, inorganic phosphate; PDE, phosphodiesters (principally glycerol 3-phosphorylcholine); PCr, phosphocreatine; ATP, adenosine 5-triphosphates.

was constant with a pulse width of one third of the normal pulse power that sampled the anterior region of the phakic and pseudophakic eye. For the ratio, we used both the peak height and the area under the peak to get more information about the quality of the data. The contribution from the lens for the phosphomonoesters signal is approximately 30% of that in the normal eye. The contribution for the adenosine triphosphates signals is approximately 15% of those in the normal phakic eye. The contribution of the phosphodiesters signal from the lens is not significant and most likely contains glycerol 3-phosphorylcholine, as demonstrated in previous studies.[6,8] The rest of the phosphomonoesters, phosphodiesters, and adenosine triphosphates signals originate mainly from the extraocular muscles, the anterior orbital fat tissue, and the cornea.

Figure 4 is the phosphorus 31 magnetic resonance spectrum of an eye with a choroidal melanoma. This right eye contained a large choroidal melanoma originating superonasally with a secondary bullous inferior retinal detachment. Three days before the in vivo spectroscopy, four tantalum rings were sutured on the sclera. The spectrum was obtained with a total pulse power to cover the tumor region.

No modification of the series of nine spectra (Figs. 5, 6, and 7) with the same normal pulse power was noted in eyes without tantalum rings or in newly operated on eyes with episcleral tantalum rings. Xenon photocoagulation on the tumor surface did not change the pattern of spectra. The presence of posterior subcapsular opacities did not modify the general profile of the phosphorus 31 magnetic resonance spectrum; we noted only a decrease of phosphocreatine and adenosine triphosphate resonance signals.

The findings in Case 10 show the phosphorus 31 magnetic resonance spectrum of an eye with a large ciliary body melanoma. The eye was enucleated three days after magnetic resonance measurements because of the large size of the tumor. Microscopic examination disclosed 70% spindle cells, balloon cell transformation, and few necrotic cells. The high phospholipid concentration and the absence of necrosis may explain the particular spectrum of this tumor, with a high sugar phosphates signal containing the phosphomonoesters band and a low inorganic phosphate signal in comparison with the other spectra.

Phosphorus 31 magnetic resonance spectra of eyes with other choroidal tumors show the same general pattern with different signal intensities (Fig. 8).

High levels of phosphodiesters, glycerol 3-phosphorylethanolamine and glycerol 3-phos-

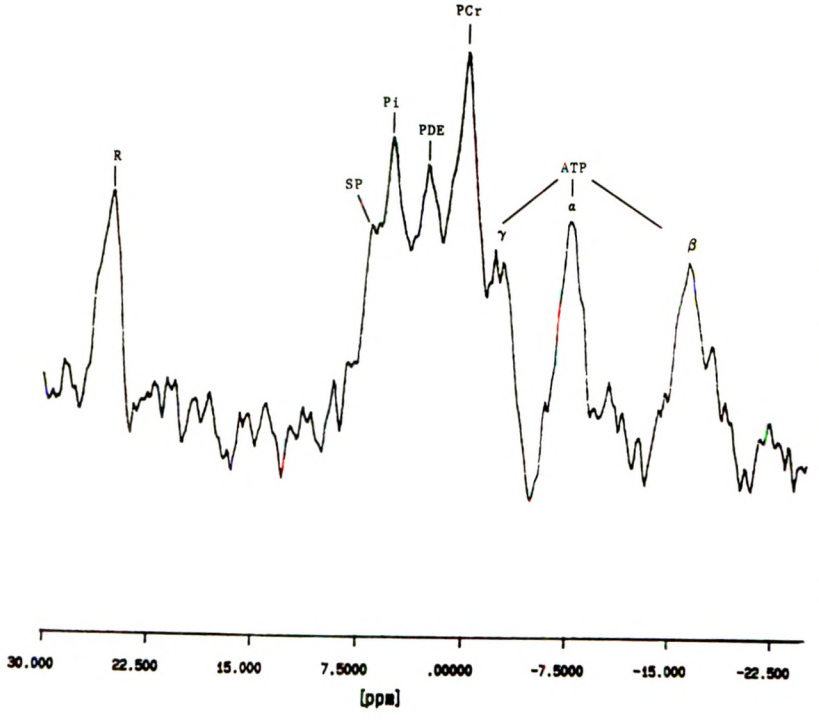


Fig. 4 (De Potter, von Weymarn, and Zografos). Case 1. In vivo phosphorus 31 magnetic resonance spectrum of a human eye containing a choroidal melanoma located anterior to the equator and associated retinal detachment obtained with a total radiofrequency pulse power. R, external reference; SP, sugar phosphates, including phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; ATP, adenosine 5-triphosphates. The phosphodiesters peak includes overlapping of glycerol 3-phosphorylethanolamine and glycerol 3-phosphorylcholine resonances.

phorylcholine, were noted in our melanoma spectra. The resolution of spectra, however, did not always allow distinction of the phosphodiesters component from the phosphodiesters peak signal. Other peaks common to all metabolically active tissues (cornea, lens, tumor, and extraocular muscles), caused by the high-energy compounds, adenosine 5-triphosphate and phosphocreatine, are also evident.

It is generally believed that mensuration data of the six extraocular muscles appear to be relatively constant in adults.[31] The resonance

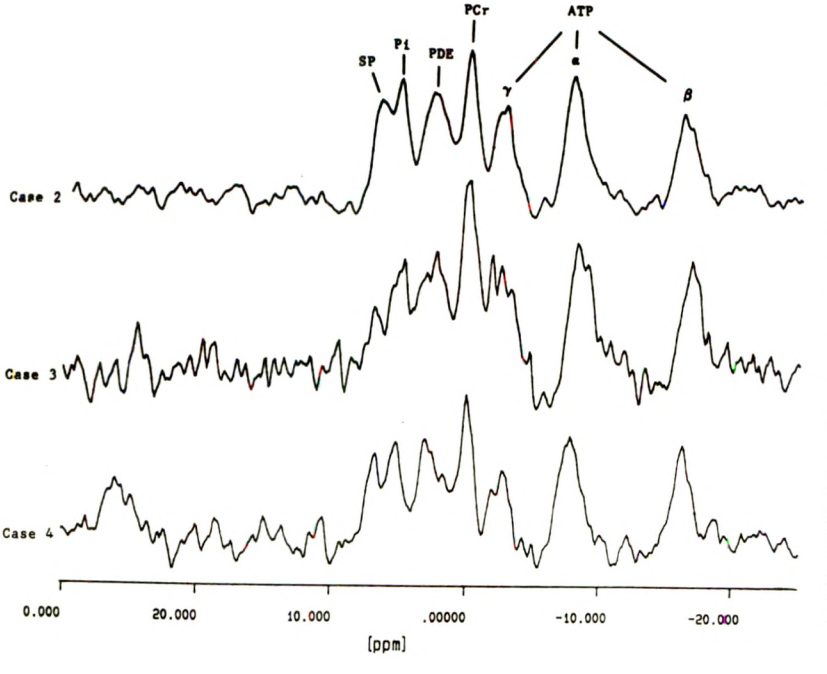


Fig. 5 (De Potter, von Weymarn, and Zografos). Case 2, first row. In vivo phosphorus 31 magnetic resonance spectrum of a human eye containing a ciliary body melanoma with lens opacities. Case 3, second row. In vivo phosphorus 31 spectrum of an eye with a choroidal melanoma located anterior to the equator. Case 4, third row. In vivo phosphorus 31 spectrum of an eye with a choroidal melanoma located in the posterior pole and an associated localized retinal detachment. These spectra were obtained with a total radiofrequency pulse power. R, external reference; SP, sugar phosphates, including phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; ATP, adenosine 5-triphosphates.

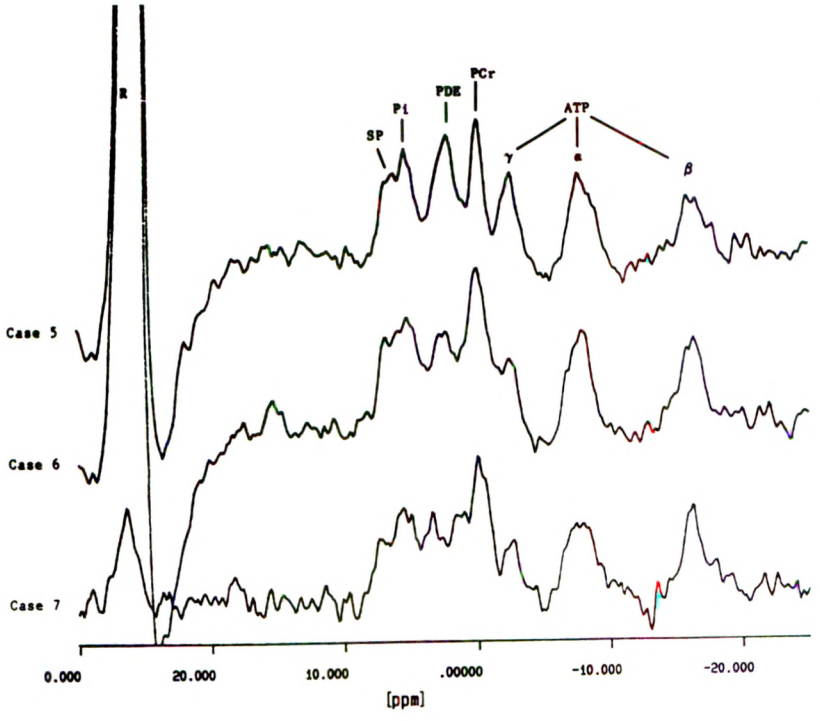


Fig. 6 (De Potter, von Weymarn, and Zografos). Case 5, first row. In vivo phosphorus 31 magnetic resonance spectrum of a human eye containing a recurrent choroidal melanoma treated previously with proton beam irradiation. Case 6, second row. In vivo phosphorus 31 spectrum of an eye with a choroidal melanoma. Case 7, third row. In vivo phosphorus 31 spectrum of an eye with a choroidal melanoma and retinal detachment. Melanomas were located in the posterior pole in the three eyes, and spectra were obtained with a total radiofrequency pulse power. R, external reference; SP, sugar phosphates, including phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; ATP, adenosine 5-triphosphates.

from phosphocreatine is of low intensity in ocular tissues[3,6] and ocular tumors such as choroidal melanoma.[25-27] Since the important contribution of the phosphocreatine signal originates from extraocular muscles in the eyelid and the orbit where the volume appears to be constant from one patient to another,[31] we compared the phosphocreatine peak intensity to that of the phosphodiesters to differentiate the intraocular tumors.

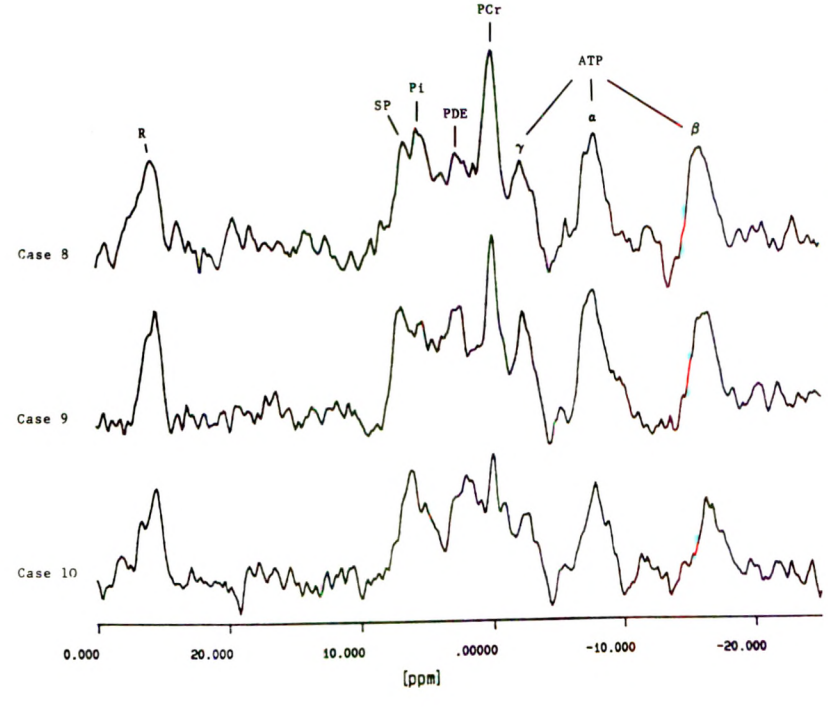


Fig. 7 (De Potter, von Weymarn, and Zografos). Case 8, first row. In vivo phosphorus 31 magnetic resonance spectrum of human eye containing a choroidal melanoma located anterior to the equator with an associated retinal detachment. Case 9, second row. In vivo phosphorus 31 spectrum of an eye with a ciliary body melanoma and retinal detachment. Case 10, third row. In vivo phosphorus 31 spectrum of an eye with a ciliary body melanoma and with retinal detachment. These spectra were obtained with a total radiofrequency pulse power. R, external reference; SP, sugar phosphates, including phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; ATP, adenosine 5-triphosphates.

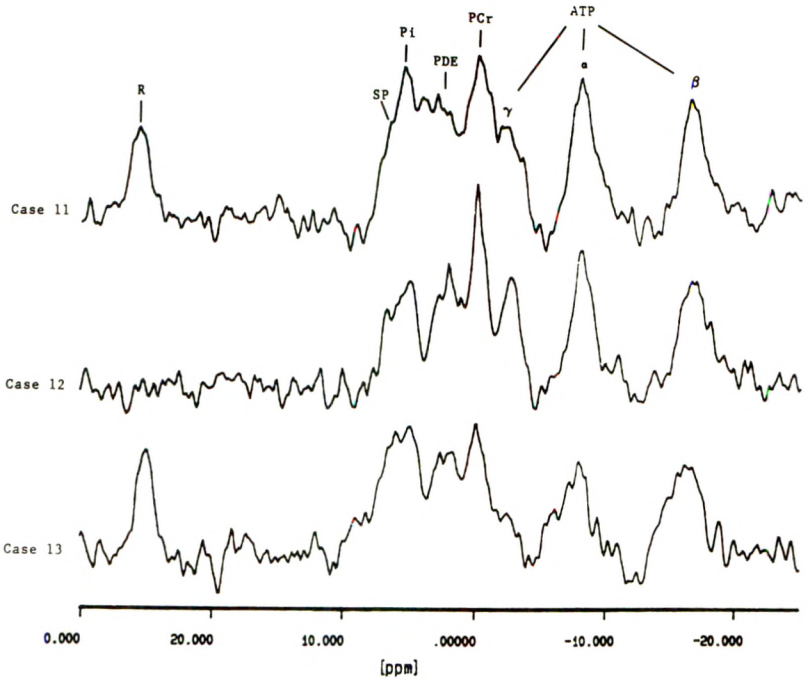


Fig. 8 (De Potter, von Weymarn, and Zografos). Case 11, first row. In vivo phosphorus 31 magnetic resonance spectrum of an eye containing a choroidal metastasis located in the posterior pole with an associated retinal detachment. Case 12, second row. In vivo phosphorus 31 spectrum of an eye with a juxtapapillary choroidal hemangioma. Case 13, third row. In vivo phosphorus 31 spectrum of human eye containing a choroidal osteoma located at the posterior pole. These spectra were obtained with a total radiofrequency pulse power. R, external reference; SP, sugar phosphates, including phosphomonoesters; Pi, inorganic phosphate; PDE, phosphodiesters; PCr, phosphocreatine; ATP, adenosine 5-triphosphates.

Phosphocreatine:phosphodiesters area values ratios in the normal phakic eye, the ten eyes with melanomas, and the three eyes with other lesions, all sampled with the normal pulse power, are shown in Table 4. The standard error for the given values came from signal-to-noise ratios of our spectra. We estimated it to be ± 9% for the ratio values. The dependence of the phosphocreatine:phosphodiesters ratio values from the estimated volume of uveal melanomas and the normal phakic eye is shown in Figure 9. By analyzing the ratio values, the concentration of phosphodiesters in a normal eye was estimated to be 30% less than in an eye with a small melanoma. All of our melanoma spectra showed low phosphocreatine:phosphodiesters ratios because of high phosphodiesters concentrations, which tend to increase with the volume of the tumor. This high phosphodiesters level was only detected in melanomas with a tumor volume larger than 0.21 ml. The phosphodiesters level in the eye with a smaller melanoma (Case 6) appeared as low as in the normal phakic eye.

The three eyes with other choroidal tumors showed low phosphocreatine:phosphodiesters ratio values (Table 4). The choroidal hemangioma with a volume of 0.27 ml compared by extrapolation to the choroidal metastasis with a volume of 0.36 ml was characterized by an increase of approximately 50% of the phosphocreatine:phosphodiesters ratio because of the lower phosphodiesters concentration in the choroidal hemangioma. The metastatic tumor (0.36 ml) compared by extrapolation with the smallest melanoma (0.46 ml) showing a detectable phosphodiesters level was characterized

TABLE 4
RATIOS OF PHOSPHOCREATINE:PHOSPHODIESTERS AREA VALUES OF TUMOR SPECTRA SAMPLED WITH A TOTAL RADIOFREQUENCY PULSE POWER

CASE NO.	TUMOR VOLUME (ML)	PHOSPHOCREATINE: PHOSPHODIESTERS
Normal	0.00	1.16±0.101
1	1.42	0.52±0.047
2	1.97	0.75±0.067
3	0.46	0.86±0.077
4	0.58	0.61±0.055
5	0.50	0.69±0.062
6	0.21	1.75±0.158
7	0.79	0.51±0.046
8	1.54	0.61±0.055
9	2.11	0.60±0.054
10	0.60	0.43±0.039
11	0.36	0.53±0.048
12	0.27	0.81±0.073
13	0.15	0.56±0.050

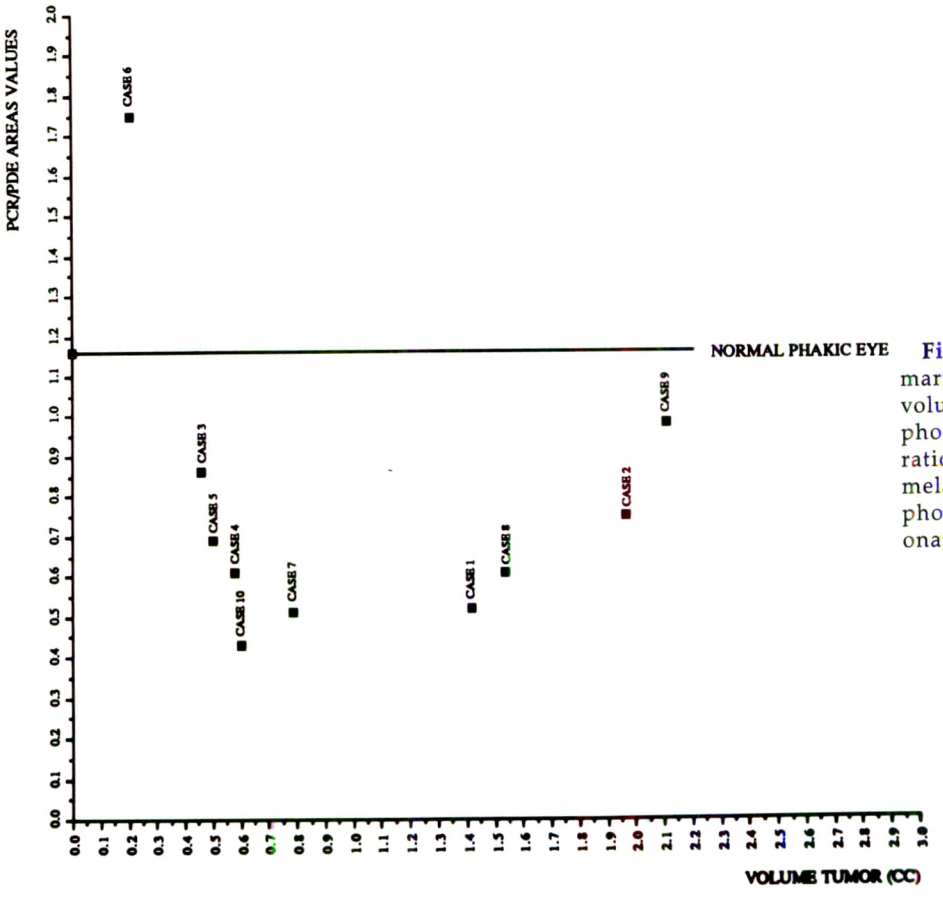


Fig. 9 (De Potter, von Weymarn, and Zografos). Tumor volume dependence of phosphocreatine:phosphodiesters ratio area values in uveal melanomas determined by phosphorus 31 magnetic resonance spectroscopy in vivo.

by an estimated decrease of 20% of the phosphocreatine:phosphodiesters ratio. However, the choroidal hemangioma (0.27 ml) compared by extrapolation with the same choroidal melanoma (0.46 ml) showed an increase of approximately 50% of this ratio. Although the choroidal osteoma (Case 13) had a volume of 0.15 ml, a phosphodiesters peak was identified in the phosphorus 31 spectrum, and the phosphocreatine:phosphodiesters ratio was different than that of a normal phakic eye. This ratio appeared to be as low as that of a choroidal melanoma that was four times larger in size.

We did not determine the chemical shift of the inorganic phosphate peak because pH analysis showed no changes overall in the patients. The small number of our patients did not allow any statistical analysis.

Discussion

Until recently, phosphorus 31 magnetic resonance spectra of ocular tumors have been obtained only on enucleated human eyes,[22,24,27,28] perfused cultured cells,[32] cultured cell pellets,[25] and tumors in athymic nude mice.[33] Kolodny and associates[27] demonstrated that the phosphorus metabolite levels in choroidal melanomas differ from those in normal human lens. All of the eyes with melanoma had increased levels of the membrane phospholipid monoesters, phosphorylethanolamine and phosphorylcholine, and phosphodiesters, glycerol 3-phosphorylethanolamine and glycerol 3-phosphorylcholine.[25,27] However, significant variation in the relative levels of the four monoester and diester compounds was observed.

To study the in vivo tumor metabolism, the spectral acquisition variables (the radiofrequency pulse power) were optimized for the ocular tumor by increasing the penetration of the exciting radiofrequency pulse with the total normal pulse power.[1,34] Moreover, by using an adiabatic pulse, the excitation range could reach to a depth of the diameter of the coil. Spectral contamination from surrounding tissues, such as the extraocular muscles in the

eyelid and the orbit, cannot be excluded (particularly for phosphocreatine and adenosine triphosphate signals) and represents the most important limitation for interpretation.

The sugar phosphate resonance band in almost all tissues exhibits three characteristic groups of signals: a band corresponding to triose phosphates, a band corresponding to hexose and pentose phosphates, and a band corresponding to phosphomonoesters, phosphorylethanolamine, and phosphorylcholine.[5-7] The trioses, hexoses, and phosphomonoesters band shows usually a complex system of overlapping resonance multiplets, which, depending on their concentration, may show prominent signals.[6] In all of our spectra, it was difficult to detect high-resolution signals from the sugar phosphate resonance band. The highest sugar phosphates signal was obtained in our only histologic specimen that showed balloon cell degeneration (Case 10).

According to Evanochko, Ng, and Glickson,[12] the varying levels of inorganic phosphate in spectra can be explained by the volume of the tumor and the vascular occlusions during fast tumor growth, which result in metabolic deprivation and increase in proportion of hypoxic cells. An increase of inorganic phosphate and decrease of phosphocreatine can then be observed. We did not find an inorganic phosphate-dominant pattern with complete loss of adenosine triphosphates, characteristic of tumor necrosis.[12,16,18] This could be explained by the contribution of the lens and extraocular muscles for the adenosine triphosphates signals. The absence of necrosis proved by microscopic examination in one eye (Case 10) may explain the small inorganic phosphate level in this spectrum.

According to Sostman, Armitage, and Fischer,[11] the peaks caused by the high-energy compounds, adenosine 5-triphosphates and phosphocreatine, have been shown to reflect the overall metabolic activity of many types of tissues. The levels of these peaks most likely reflect the viability of probably well-vascularized and predominantly aerobic tumor with most of adenosine triphosphates being generated by oxidative phosphorylation and phosphocreatine being the storage form of high-energy phosphates.[11,12] Damage to tumor vasculature might result in decreased blood flow that would also lead to rapid decrease in phosphocreatine and adenosine triphosphates.[11,16-18] Since the phosphocreatine peak is always small or not visible in different types of human malignant tumors[13,16,18,19] and the phosphocreatine signal is attributed primarily to contributions from surrounding extraocular muscles, this metabolite does not represent any significant tumor component to evaluate the aerobic metabolism.

The most prominent feature of choroidal melanomas and other choroidal tumors in in vivo phosphorus 31 magnetic resonance spectra appears to have a major component: the phosphodiesters peak. Because of the spectra resolution, this resonance band from phosphodiesters shows a unique prominent peak with overlapping resonances from glycerol 3-phosphorylethanolamine and glycerol 3-phosphorylcholine. Conversely, the resonance from phosphodiesters in spectra of the normal phakic and pseudophakic eye is identified as being principally assigned to glycerol 3-phosphorylcholine.[6,8] We did not find the other high identifiable level of phosphomonoesters, phosphorylethanolamine and phosphorylcholine, which were detected in uveal melanoma cells and melanoma in enucleated eyes, as markers of the uveal melanoma cells.[25-27] The poor resolution of our spectra in sugar phosphates, phosphomonoesters, and inorganic phosphate regions, however, makes any identification of these compounds difficult. The only spectrum that had a high-resonance signal from the sugar phosphates (phosphomonoesters) is observed when balloon cell transformation was seen on histologic examination. Thus, two conditions are necessary to show high identifiable peaks: high concentration of the compound in the tumor in vivo and high signal-to-noise ratio.

As reported by Sostman, Armitage, and Fischer,[11] Proietti and associates,[35] and Carpinelli and associates,[36] phosphodiesters may be involved in phospholipid catabolism, and phosphomonoesters are involved in phospholipid synthesis. It is then possible that their proportion may reflect rates of membrane synthesis and catabolism. Studies using phosphorus 31 magnetic resonance in Friend leukemia cells subcutaneously implanted in mice[37] have shown significant increase in phosphodiesters with growth of tumor mass and have speculated that this increase of phosphodiesters levels may reflect membrane catabolism in cells undergoing ischemic injury. The modulations in the phosphodiesters levels are suggested as possible markers for monitoring conditions of growth, differentiation, and proliferative capability of cells.[36,37] Since the contribution of the phosphodiesters signal from muscle spectra is

low and from surrounding tissues is constant, we believe that phosphodiesters may represent a useful variable with which to identify the tumor.

Because phosphocreatine does not represent any ocular tumor component[25-27] and because of its relatively constant contribution from surrounding extraocular muscles in the eyelid and the orbit,[31] we compared the ratio of phosphocreatine to phosphodiesters area values to identify choroidal tumors that show lower ratio values because of higher concentrations of phosphodiesters than those of the normal phakic eye. This high phosphodiesters level was only detected in choroidal melanomas with a volume greater than 0.21 ml (Fig. 9). Uveal melanomas and the choroidal metastasis had higher phosphodiesters concentration than that of benign choroidal tumors. This could be explained by the proliferative capability of malignant cells and their higher phospholipid metabolism.[37] The choroidal hemangioma with a volume of 0.27 ml compared by extrapolation to the choroidal metastasis (0.36 ml) and the smallest melanoma (0.46 ml) with a detectable phosphodiesters level was characterized by an increase of approximately 50% of the phosphocreatine:phosphodiesters ratio because of the lower phosphodiesters level. However, it appeared that the choroidal metastasis (0.37 ml) compared by extrapolation to this choroidal melanoma (0.46 ml) had a higher phosphodiesters concentration. This could be explained by the more aggressive proliferative potential of metastatic cells than melanocytic cells.

We were surprised to find such a high phosphodiesters level in the spectrum of the small choroidal osteoma, which is a benign tumor. Choroidal osteoma has been reported to appear as a bright signal on T_1-weighted images and dark signal on T_2-weighted scans (unpublished data). It was postulated that the high concentration of phosphodiesters metabolites accumulated in the intertrabecular fat marrow explains these magnetic resonance imaging features. Melanoma with a volume less than 0.21 ml could not show phosphodiesters signal high enough to be distinguished from the normal phakic eye. The phosphodiesters concentration increased with the volume of the melanoma, which may have resulted from the different stages of growth, since the tumor doubling times, the tumor growth rate, and histologic examination in our cases are unknown. The amount of inorganic phosphate was not considered as a useful variable, because it is influenced by the body's ability to remove anoxic cells from the tumor.[13]

The absence of artifacts from the tantalum rings was explained by the nonmagnetic property of pure tantalum.[38,39] No changes in the phosphorus 31 magnetic resonance profiles of eyes with or without rings were found.

Xenon photocoagulation therapy performed to decrease the tumor exudation is effective only on the superficial regions of the tumor and after two or three weeks.[40,41] This could explain the lack of changes in the spectra of the treated eyes.

These preliminary data on the potential applications of in vivo phosphorus 31 magnetic resonance spectroscopy for the differential diagnosis of intraocular tumors are promising despite spectra contamination from surrounding tissues inherent in the surface coil probe and the small number of cases. New techniques to increase detection sensitivity and exclusion of signal contamination from surrounding tissue, such as chemical shift imaging,[16,19] will have to be found for better interpretation of phosphorus 31 magnetic resonance spectra. The feasibility of using in vivo magnetic resonance spectroscopy to determine cell types, to study the tumor response to irradiation by analyzing aerobic metabolism of the tumor, and to predict the prognostic factors for the development of metastasis warrants further research.

References

1. Gadian, D. G.: Nuclear Magnetic Resonance and its Applications to Living Systems. Oxford, Clarendon, 1982.

2. Akerman, J. J., Grove, T. H., Gadian, D. G., and Radda, G. K.: Mapping of metabolites by phosphorus 31 nuclear magnetic resonance using surface coils. Nature. 283:167, 1980.

3. Greiner, J. V., Kopp, S. J., Gillette, T. E., and Glonek, T.: Phosphatic metabolites of the intact cornea by phosphorus 31 nuclear magnetic resonance. Invest. Ophthalmol. Vis. Sci. 24:535, 1983.

4. Greiner, J. V., Kopp, S. J., and Glonek, T.: Nondestructive metabolic analysis of a cornea with the use of phosphorus nuclear magnetic resonance. Arch. Ophthalmol. 102:770, 1984.

5. Greiner, J. V., Lass, J. H., and Glonek, T.: Ex vivo metabolic analysis of eye bank corneas using phosphorus nuclear magnetic resonance. Arch. Ophthalmol. 102:1171, 1984.

6. Greiner, J. V., Kopp, S. J., Sanders, D. R., and Glonek, T.: Organophosphates of the crystalline

lens. A nuclear magnetic resonance study. Invest. Ophthalmol. Vis. Sci. 21:700, 1981.

7. Kopp, S. J., Glonek, T., and Greiner, J. V.: Interspecies variations in mammalian lens metabolites as detected by phosphorus 31 nuclear magnetic resonance. Science 215:1622, 1982.

8. Schleich, T., Willis, J. A., and Matson, G. B.: Longitudinal (T1) relaxation times of phosphorus metabolites in the bovine and rabbit lens. Exp. Eye Res. 39:455, 1984.

9. Willis, J. A., and Schleich, T.: The effect of prolonged elevated glucose levels on the phosphate metabolism of the rabbit lens in perfused organ culture. Exp. Eye Res. 43:329, 1986.

10. Chapman, D., Kemp, C. M., Morris, P. G., and Pons, M.: Studies on cellular metabolism in isolated intact bovine retinas by phosphorus 31 nuclear magnetic resonance. FEBS Lett. 143:293, 1982.

11. Sostman, H. D., Armitage, I. M., and Fischer, J. J.: Nuclear magnetic resonance in cancer. I. High resolution spectroscopy of tumors. Magn. Reson. Imaging 2:265, 1984.

12. Evanochko, W. T., Ng, T. C., and Glickson, J. D.: Application of in vivo nuclear magnetic resonance spectroscopy in cancer. Magn. Reson. Med. 1:508, 1984.

13. Nidecker, A. C., Muller, S., Aue, W. P., Seelig, J., Fridrich, R., Remagen, W., Hartweg, H., and Benz, U. F.: Extremity bone tumors. Evaluation by phosphorus 31 magnetic resonance spectroscopy. Radiology 157:167, 1985.

14. Zimmerman, R. A., Bottomley, P. A., Edelstein, W. A., Hart, H. R., Redington, R. W., Bilaniuk, L. T., Grossman, R. I., Goldberg, H. I., Bruno, L., and Kressel, H.: Proton imaging and phosphorus spectroscopy in malignant glioma. AJNR 6:109, 1985.

15. Marincek, B., and Friedburg, H.: Calculated T1 and T2 magnetic resonance images and phosphorus 31 magnetic resonance spectra in rabbit thigh V2 carcinoma to monitor the effect of steroid administration. Invest. Radiol. 20:701, 1985.

16. Naruse, S., Hirakawa, K., Horikawa, Y., Tanaka, C., Higuchi, T., Ueda, S., Nishikawa, H., and Watari, H.: Measurements of in vivo phosphorus 31 nuclear magnetic resonance spectra in neuroectodermal tumors for the evaluation of the effects of chemotherapy. Cancer Res. 45:2429, 1985.

17. Okunieff, P. G., Koutcher, J. A., Gerwek, L., McFarland, E., Hitzig, B., Urano, M., Brady, T., Neuringer, L., and Suit, H. D.: Tumor size dependent changes in murine fibrosarcoma. Use of in vivo phosphorus 31 nuclear magnetic resonance for non-invasive evaluation of tumor metabolic status. Int. J. Radiat. Oncol. Biol. Phys. 12:793, 1986.

18. Naruse, S., Horikawa, Y., Tanaka, C., Higuchi, T., Sekimoto, H., Ueda, S., and Hirakawa, K.: Evaluation of the effects of photoradiation therapy on brain tumors with in vivo phosphorus 31 magnetic resonance spectroscopy. Radiology 160:827, 1986.

19. Degani, H., Horowitz, A., and Itzchak, Y.: Breast tumors. Evaluation with phosphorus 31 magnetic resonance spectroscopy. Radiology 161:53, 1986.

20. Griffiths, J. R., Rodrigues, L., and Stuubs, M.: The significance of high energy phosphorus metabolites in tumors. In Society of Magnetic Resonance in Medicine. Sixth Annual Meeting and Exhibition, vol. 2, 1987, p. 33.

21. D'Amico, D. J., Kolodny, N. H., and Gragoudas, E. S.: Phosphorus 31 nuclear magnetic resonance spectra of ocular melanoma in rabbits. Metabolic correlates of proton-beam induced tumor regression. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1985, p. 209.

22. Gomori, J. M., Grossman, R. I., Shields, J. A., Augsburger, J. J., Joseph, P. M., and DeSimeone, D.: Choroidal melanomas. Correlation of nuclear magnetic resonance spectroscopy and magnetic resonance imaging. Radiology 158:443, 1986.

23. Greiner, J. V., Kopp, S. J., and Glonek, T.: Phosphorus nuclear magnetic resonance and ocular metabolism. Surv. Ophthalmol. 30:189, 1985.

24. Kindy-Degnan, N., Murray, T., Char, D. H., Swift, P., Kurhanewicz, J., and Kaleta S.: Assessment of intraocular tumor viability. A pre- and post-treatment comparison of fine needle biopsy and phosphorus 31 nuclear magnetic resonance spectroscopy. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 210.

25. Kolodny, N. H., Albert, D. M., Epstein, J., Ruzzo, M., and Sprengnether, M.: Characterization of human uveal melanoma cells by phosphorus 31 nuclear magnetic resonance spectroscopy. Am. J. Ophthalmol. 100:38, 1985.

26. Kolodny, N. H., Gragoudas, E. S., and D'Amico, D. J.: Multinuclear magnetic resonance imaging and spectroscopy of human ocular tumors. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis Sci. Philadelphia, J. B. Lippincott, 1987, p. 116.

27. Kolodny, N. H., Gragoudas, E. S., D'Amico, D. J., Seddon, J. M., Minichello, M., Murphy, E. L., and Albert, D. M.: Preliminary results on phosphorus 31 nuclear magnetic resonance evaluation of human uveal melanoma in enucleated eyes. Ophthalmology 95:666, 1988.

28. Kolodny, N. H., Svitra, P. P., and Gragoudas, E. S.: In vivo phosphorus 31 nuclear magnetic resonance spectroscopy of rabbit choroidal melanoma. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1986, p. 259.

29. Kolodny, N. H., Gragoudas, E. S., D'Amico, D. J., and Albert, D. M.: Magnetic resonance imaging and spectroscopy of intraocular tumors. Surv. Ophthalmol. 33:502, 1989.

30. Murphy-Boesch, J., and Koretsky, A. P.: An in vivo nuclear magnetic resonance probe circuit for improved sensitivity. J. Magn. Reson. 54:526, 1983.

31. Eggers, H. M.: Functional anatomy of the extraocular muscles. In Jakobiec, F. A.: Ocular Anatomy, Embryology, and Teratology. Philadelphia, Harper and Row, 1988, pp. 783–834.

32. Minichiello, M., Albert, D. M., and Kolodny, N. H.: Phosphorus-31 magnetic resonance spectroscopy monitoring of human ocular melanoma metabolism employing a perfusion culture system. ARVO abstracts. Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1987, p. 25.

33. Albert, D. M., Svitra, P. P., and Kolodny, N. H.: Phosphorus 31 nuclear magnetic resonance spectroscopy of human ocular tumors in athymic mice. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1986, p. 86.

34. Schleich, T., Matson, G. B., Willis, J. A., Acosta, G., Serdahl, C., Campbell, P., and Garwood, M.: Surface coil phosphorus 31 nuclear magnetic resonance studies of the intact eye. Exp. Eye Res. 40:343, 1985.

35. Proietti, E., Carpinelli, G., Di Vito, M., Belardelli, F., Gresser, I., and Podo, F.: Phosphorus 31 nuclear magnetic resonance analysis of interferon-induced alterations of phospholipid metabolism in interferon-sensitive and interferon-resistant Friend leukemia cell tumors in mice. Cancer Res. 46:2849, 1986.

36. Carpinelli, G., Maddaluno, G., Podo, F., and Proietti, E.: Phosphorus 31 nuclear magnetic resonance studies on subcutaneous tumors in mice injected with Friend erythroleukemia cells. Magn. Reson. Med. 1:12, 1984.

37. Carpinelli, G., Podo, F., Di Vito, M., Proietti, E., Gessani, S., and Belardelli, F.: Modulations of glycerophosphorylcholine and phosphorylcholine in Friend erythroleukemia cells upon vitro-induced erythroid differentiation. FEBS Lett. 176:88, 1984.

38. Smith, E. V., Kolodny, N. H., Gragoudas, E. S., Rubin, L. G., Seddon, J. H., and D'Amico, D. J.: Safety and effectiveness of magnetic resonance imaging of choroidal melanoma patients with episcleral tantalum rings after proton beam irradiation. Am. J. Ophthalmol. 105:695, 1988.

39. Zheutlin, J. D., Thompson, J. T., and Shofner, R. S.: The safety of magnetic resonance imaging with intraorbital metallic objects after retinal reattachment or trauma. Am. J. Ophthalmol. 103:831, 1987.

40. Lund, O. E.: Changes in choroidal tumors after light coagulation. Arch. Ophthalmol. 75:458, 1966.

41. Vogel, M. H.: Treatment of malignant choroidal melanomas with photocoagulation. Am. J. Ophthalmol. 74:1, 1972.

OPHTHALMIC MINIATURE

She had intended to say "Whose boy are you?" but she said nothing, her mouth opening on a vanished sentence. His eyes as they turned and looked down at her were the color of the lake just before dark when the last daylight has faded and the moon has not risen yet, and for an instant she thought she saw something fleeing across the surface of them, a lost light that came from nowhere and vanished into nothing.

Flannery O'Connor, *The Violent Bear It Away*
New York, Farrar, Straus & Cudahy, 1955, p. 156

Prevalence and Association of Asteroid Hyalosis With Systemic Diseases

Robert L. Bergren, M.D., Gary C. Brown, M.D., and Jay S. Duker, M.D.

We performed a cross-sectional study of 12,205 patients, which identified 101 patients (0.83%) with asteroid hyalosis. These patients were examined for associated systemic and ocular conditions. Diabetes mellitus was found in 29 of the patients with asteroid hyalosis (29%), as compared to ten of 101 (10%) control subjects (P = .0007). An increased prevalence of systemic arterial hypertension (61 of 101 [60%] patients with asteroid hyalosis compared with 29 of 101 [29%] control subjects; P = .0001) and atherosclerotic vascular disease (30 of 101 [30%] patients with asteroid hyalosis compared with 13 of 101 [13%] control subjects; P = .006) was also discovered in the asteroid hyalosis group. Additionally, patients with asteroid hyalosis were found to be more hyperopic than control subjects (P = .009).

Asteroid hyalosis was first described and differentiated from synchysis scintillans by Benson[1] in 1894. At that time, he used the term asteroid hyalitis because the particles resembled "stars on a clear night." Because there is no evidence of inflammation with this condition, Luxenberg and Sime[2] suggested the currently accepted term, asteroid hyalosis. Since its description, a number of studies have suggested a relationship between asteroid hyalosis and systemic conditions, including hypercholesterolemia, hyperlipidemia, hypercalcemia, and diabetes mellitus. Nevertheless, no ocular or systemic condition has been consistently associated with asteroid hyalosis.

Several studies have reported a possible association between asteroid hyalosis and diabetes mellitus. The prevalence of diabetes in patients with asteroid hyalosis was found to be 25% (13 of 52 patients) by Wasano and associates,[3] 19% (six of 32 patients) by Smith,[4] 33% (six of 18 patients) by Agarwal and associates,[5] 28% (nine of 32 patients) by Hatfield, Gastineau, and Rucker,[6] and 27% (seven of 26 patients) by Bard.[7] A follow-up study by Smith[8] found a prevalence of 66% (40 of 60 patients) using glucose tolerance testing with strict criteria. The prevalence of diabetes in all of these studies is similar, except for the second study by Smith.[8] The cumulative prevalence of diabetes in these studies is 37% (81 of 220 patients) or 26% (41 of 160 patients) when the second study by Smith is excluded. All of these studies were uncontrolled, and some were taken from a referral-based population. Additionally, diabetes mellitus was variably defined either by history, fasting blood glucose, or glucose tolerance testing.

Luxenberg and Sime[2] attempted to resolve the problems of these previous studies and performed a controlled, primarily general clinic–based study. They reported the prevalence of diabetes in patients with asteroid hyalosis as 4% (four of 98 patients) by history and 41% (40 of 98 patients) by glucose tolerance testing or history. The prevalence of diabetes in their control group was 4% (four of 98 patients) by history and 45% (44 of 98 patients) by glucose tolerance testing or history. There are two concerns with this study. First, the prevalence of 4% by history seems remarkably low when compared to the several previously reported series. Second, the prevalence of abnormal glucose tolerance test results in more than 40% of subjects in both the study and control groups raises questions as to the significance of these tests in this population, as pointed out by Luxenberg and Sime. This study, however, is widely quoted as evidence that asteroid hyalosis is not preferentially associated with diabetes mellitus.

We attempted to further clarify the relation-

Accepted for publication Dec. 19, 1990.

From the Retina Vascular Unit, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania. This study was supported in part by the Retina Research and Development Fund, Philadelphia, Pennsylvania.

Reprint requests to Gary C. Brown, M.D., 910 E. Willow Grove Ave., Wyndmoor, PA 19118.

ship of asteroid hyalosis to diabetes mellitus and other systemic conditions. We rely on controlled historical data from one clinic.

Patients and Methods

All consecutive patients who underwent a routine examination with pupillary dilation at the Primary Eye Care Service of Wills Eye Hospital between August 1989 and March 1990 were included. The examination of all patients consisted of a detailed history of previous ocular and systemic disease on a standard form. Specific questions concerning diabetes mellitus, systemic arterial hypertension, atherosclerotic vascular disease (history of angina, heart attack, or stroke), and medications were recorded routinely by ophthalmic technicians before ocular examination of all patients during the study period. Only patients with a history of systemic arterial hypertension who were currently receiving treatment with a recognized antihypertensive medication were classified as hypertensive. Additionally, all patients were examined with slit-lamp biomicroscopy and had a known refractive error.

Asteroid hyalosis was diagnosed by resident physicians who were specifically asked to screen for this entity. Those patients with any evidence of the abnormality, however mild, were included. Junior residents were requested to review the diagnosis with a senior resident or faculty if there was any question regarding the diagnosis. Resident physicians were required routinely to record patient information on a daily tally sheet, and a column specifically regarding asteroid hyalosis was present on this sheet during the study period.

The control group consisted of 101 patients from the same population. On three separate randomly chosen days during the predesignated study period, the charts of control subjects were reviewed and were selected by age to match the patients. Patients were separated into five-year age groups. Consecutive charts on these days were accepted into the control group if they received a routine examination with pupillary dilation and their age fell into a five-year age group that was not previously filled. The person selecting the control subjects reviewed only the age of the potential control subjects and whether or not they had a fundus examination. Statistical analyses were performed using the chi-square analysis. The unpaired *t*-test was also used.

Results

Of 12,205 subjects, 101 (0.83%) were noted to have asteroid hyalosis. Asteroid hyalosis was unilateral in 82 patients (81%). In these 82 patients, 40 (49%) had involvement of the right eye, whereas the left eye was affected in 42 (51%).

The clinical characteristics of the asteroid hyalosis group and the control group were similar. The average age of patients in both groups was approximately 70 years. The age range of patients with asteroid hyalosis was 35 to 97 years. Of the patients with asteroid hyalosis, 52 were women, 49 were men, 52 were white, and 49 were black. In the control group, 44 were men, 57 were women, 44 were black, and 57 were white. None of these differences were statistically significant.

Of 101 patients with asteroid hyalosis, 29 (29%) had a history of diabetes mellitus, as compared to ten of 101 control subjects (10%). This difference was statistically significant by chi-square analysis ($P = .0007$). Of 29 patients with diabetes and asteroid hyalosis, 13 were taking insulin, 13 were taking oral agents, and three were on a controlled diet alone. Of the ten control subjects with diabetes, two were taking insulin, six were taking oral agents, and two were on a controlled diet. These differences in control of diabetes were not significant. Diabetic retinopathy was found in nine of the 29 patients with asteroid hyalosis and diabetes. Of the nine patients with diabetic retinopathy, five had mild background changes only, one had background changes with macular edema, and three had proliferative diabetic retinopathy. None of the ten patients with diabetes in the control group had ophthalmoscopically visible diabetic retinopathy.

Systemic arterial hypertension was found in 61 of 101 (60%) patients with asteroid hyalosis, as compared to 29 of 101 (29%) control subjects. This difference was statistically significant by chi-square analysis ($P = .0001$). Atherosclerotic vascular disease was present in 30 of 101 (30%) patients with asteroid hyalosis, as compared to 13 of 101 (13%) control subjects. This was also statistically significant by chi-square analysis ($P = .006$).

The average refractive error of patients with asteroid hyalosis was +1.10 diopters, as compared to +0.193 diopters in the control group. This difference was statistically significant using an unpaired *t*-test ($P = .009$). The distri-

bution of refractive errors is shown in the Figure.

Discussion

Our findings confirm a relationship between asteroid hyalosis and diabetes mellitus, which contradicts the previous controlled study on asteroid hyalosis and diabetes by Luxenberg and Sime.[2] The difficulty with any inquiry involving diabetes is, of course, defining diabetes. The use of glucose tolerance testing, as performed by Luxenberg and Sime,[2] may not be appropriate. In 1979, the National Diabetes Data Group of the National Institutes of Health provided revised criteria for the diagnosis of diabetes with glucose tolerance testing.[9] These new criteria question the validity of previous studies using oral glucose tolerance testing.[9,10] Several large studies have shown that most patients with impaired glucose tolerance and a normal fasting blood glucose level never develop diabetes and may never manifest fasting hyperglycemia or symptomatic deterioration.[10] The difference seen with historical data alone is also not a perfect method because more false-negatives are incurred. Theoretically, taking control subjects from the same population as the study group helps to negate the effect of false-negatives.

Asteroid hyalosis is also apparently related to systemic vascular disease. The prevalence of systemic arterial hypertension in 60% (61 of 101) of patients with asteroid hyalosis is considerable, even with the prevalence in the control group being as high as 29% (29 of 101). This increased prevalence of hypertension and diabetes also correlates with an increased prevalence of atherosclerotic vascular disease. Whether atherosclerotic disease is truly a primary association, or simply more prevalent because of the concomitance of diabetes mellitus and hypertension, is uncertain because the number of patients in our study was insufficient for multivariate analysis. Given these results, we recommend that patients who have asteroid hyalosis and have had no recent systemic examination should at least have their blood pressure checked. Blood glucose testing should also be considered if the patient is not known to be diabetic.

Asteroid hyalosis is clearly related to an aging process, since it is rarely seen in patients younger than 50 years of age. Our data suggest that this process may be augmented by vascular and microvascular changes. Ultrastructural studies by Streeten,[11] Topilow and associates,[12] and Miller and associates[13] have shown that asteroid bodies are composed of multilaminar phospholipids associated with calcium-phosphate complexes, which are attached to normal vitreous strands. When comparing small asteroid bodies to large ones, it appears that asteroid bodies are built up by deposition of successive layers of phospholipids. The relatively acellular vitreous is unlikely to have sufficient intrinsic phospholipid for these bodies. Streeten[11] has therefore postulated that exogenous cell products, such as from inflammation, hemorrhage, or leakage from adjacent vessels, may be the source of phospholipid and calcium for asteroid formation. Diabetes mellitus,[14] systemic arterial hypertension,[15] and atherosclerosis[16] can all predispose retinal vessels to damage and subsequent leakage.

Younger patients with asteroid hyalosis often have associated ocular disease. In the youngest patient in this study, aged 35 years, asteroid hyalosis was present bilaterally, in conjunction with bilateral retinal vein occlusions. This pa-

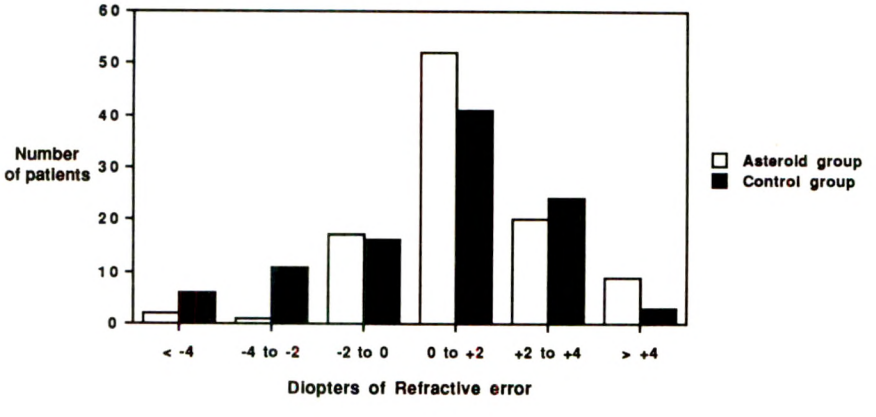


Figure (Bergren, Brown, and Duker). Distribution of refractive errors in patients with asteroid hyalosis compared to control subjects.

tient did not have diabetes mellitus, systemic arterial hypertension, or evidence of systemic vascular disease, and the cause of the retinal vein occlusions was unknown. An 11-year-old boy was described with Alstrom's syndrome who had associated bilateral retinal pigment epithelial degeneration, a flat electroretinogram, diabetes, and unilateral asteroid hyalosis.[17] In a report of a kindred of three children and a mother, asteroid hyalosis was found unilaterally in eyes with severe myopia, retinal thinning, and decreased vision. Their fellow eyes without asteroid hyalosis did not have retinal thinning.[18] Possibly, the development of asteroid hyalosis in these patients was associated with retinal degeneration and the release of cellular products, such as phospholipids and calcium.

Our data show that asteroid hyalosis is associated with a more hyperopic refractive error. The significance of this relationship is uncertain. This is a comparison of refractive errors from two groups, which may not represent the refractive error of the general population. Since asteroid hyalosis is not a symptomatic condition, both groups presumably were initially examined for similar reasons. Patients with asteroid hyalosis, however, may be more likely to have a routine examination because they are more likely to have diabetes mellitus.

The distribution of refractive errors in the Figure shows that patients with asteroid hyalosis seldom have a moderate or severely myopic refractive error. Only three of 101 patients with asteroid hyalosis had myopia of greater than 2 diopters, as compared to 17 of 101 control subjects. Wasano and associates[3] and Topilow and associates[12] showed that patients with asteroid hyalosis were less likely to have a detachment of their posterior vitreous, and if their vitreous was detached, the detachment was more likely to be partial. Wasano and associates[3] concluded that asteroid hyalosis has a protective effect on vitreous liquefaction, which prevents posterior vitreous detachment. An alternative explanation is that the posterior vitreoretinal interface may be important for the formation of asteroid hyalosis. Therefore, individuals who maintain an attached posterior vitreous to an older age are more likely to develop asteroid hyalosis. This theory could explain why asteroid hyalosis is less frequently observed in patients with moderate to severe myopia, since posterior vitreous detachment is more common and occurs at an earlier age in this group.[19]

ACKNOWLEDGMENT

Hyman Menduke, Ph.D., Department of Epidemiology and Biostatistics, Thomas Jefferson University School of Medicine, Philadelphia, Pennsylvania, provided the statistical analyses.

References

1. Benson, A. H.: Diseases of the vitreous. A case of monocular asteroid hyalitis. Trans. Ophthalmol. Soc. U. K. 14:101, 1894.

2. Luxenberg, M., and Sime, D.: Relationship of asteroid hyalosis to diabetes mellitus and plasma lipid levels. Am. J. Ophthalmol. 67:406, 1969.

3. Wasano, T., Hirokawa, H., Tagawa, H., Trempe, C. L., and Buzney, S. M.: Asteroid hyalosis. Posterior vitreous detachment and diabetic retinopathy. Ann. Ophthalmol. 19:255, 1987.

4. Smith, J. L.: Asteroid hyalitis. Incidence of diabetes mellitus and hypercholesterolemia. JAMA 168:891, 1958.

5. Agarwal, L. P., Mohan, M., Khosla, P. K., and Gupta, A. K.: Synchysis scintillans or asteroid bodies. Orient. Arch. Ophthalmol. 1:167, 1963.

6. Hatfield, R. E., Gastineau, C. F., and Rucker, C. W.: Asteroid bodies in the vitreous. Relationship to diabetes and hypercholesterolemia. Proc. Mayo Clin. 37:513, 1962.

7. Bard, L. A.: Asteroid hyalitis. Relationship to diabetes and hypercholesterolemia. Am. J. Ophthalmol. 58:239, 1964.

8. Smith, J. L.: Asteroid hyalitis and diabetes mellitus. Trans. Am. Acad. Ophthalmol. Otolaryngol. 69:269, 1965.

9. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28:1039, 1979.

10. Foster, D. W.: Diabetes mellitus. In Braunwald, E. (ed.) : Harrison's Principles of Internal Medicine, ed. 11. New York, McGraw-Hill, 1987, pp. 1778–1797.

11. Streeten, B. W.: Vitreous asteroid bodies. Ultrastructural characteristics and composition. Arch. Ophthalmol. 100:969, 1982.

12. Topilow, H. W., Kenyon, K. R., Takahashi, M., Freeman, H. M., Tolentino, F. I., and Hanninen, L. A.: Asteroid hyalosis. Biomicroscopy, ultrastructure, and composition. Arch. Ophthalmol. 100:964, 1982.

13. Miller, H., Miller, B., Rabinowitz, H., Zonis, S., and Nir, I.: Asteroid bodies. An ultrastructural study. Invest. Ophthalmol. Vis. Sci. 24:133, 1983.

14. Benson, W. E., Brown, G. C., and Tasman, W. S.: Diabetes and Its Ocular Complications. Philadelphia, W. B. Saunders, 1988, pp. 60–89.

15. Gass, J. D. M.: A flourescein angiographic study of macular dysfunction secondary to retinal

vascular disease. III. Hypertensive retinopathy. Arch. Ophthalmol. 80:569, 1968.

16. Brown, G. C., and Magargal, L. E.: The ocular ischemic syndrome. Clinical, fluorescein angiographic and carotid angiographic features. Int. Ophthalmol. 11:239, 1988.

17. Sebag, J., Albert, D. M., and Craft, J. L.: The Alstrom syndrome. Ophthalmic histopathology and retinal ultrastructure. Br. J. Ophthalmol. 68:494, 1984.

18. Beighton, P., Goldberg, L., and Op't Hof, J.: Dominant inheritance of multiple epiphyseal dysplasia, myopia and deafness. Clin. Genet. 14:173, 1978.

19. Jaffe, N. S.: Vitreous detachments. The Vitreous in Clinical Ophthalmology. St. Louis, C. V. Mosby, 1969, pp. 83–98.

OPHTHALMIC MINIATURE

Without my eyeglasses, I have a great deal of trouble distinguishing between house fires and beer signs. I wear the kind of glasses that they never show in those eyeglasses advertisements where the lenses are obviously fake because they don't distort the attractive model's face at all. My lenses make the entire middle of my head appear smaller. When professional photographers take my picture, they always suggest that I take my glasses off, because otherwise the picture shows this head with the normal top and bottom, but in the middle there's this little perfect miniature human head, maybe the size of an orange, staring out from behind my glasses.

Dave Barry, *Dave Barry's Greatest Hits*
New York, Fawcett Columbine, 1988, p. 24

Hereditary Hemorrhagic Macular Dystrophy

Gloria Wu, M.D., Ronald C. Pruett, M.D., John Baldinger, M.D., and Tatsuo Hirose, M.D.

We treated two brothers who had a hemorrhagic macular lesion in one eye; a similar problem affected the fellow eye of both patients within eight months. Generalized fine granularity of the retinal pigment epithelium and peripheral iris transillumination defects were observed in both siblings. A study of the family suggested that the disorder was dominantly inherited and probably was Sorsby's pseudoinflammatory macular dystrophy. The macular lesions in one brother were treated by argon green laser photocoagulation and in the other brother by krypton red laser photocoagulation. Although the brother treated by krypton red laser photocoagulation attained better final visual function, additional differences in treatment methods also may have contributed to the final outcome.

In 1949, Sorsby, Joll Mason, and Gardener[1] described an autosomal dominant macular dystrophy they termed pseudoinflammatory because the lesions resembled inflammatory scarring. The onset of the condition was in the third and fourth decades of life. In the early stage, acute visual loss was caused by macular hemorrhage, exudation, and edema. Later fundus characteristics included continued exudation, cicatrization, and pigmentary changes. Finally, atrophy of the retinal pigment epithelium occurred with exposure of the large choroidal vessels.

In 1978, Carr, Noble, and Nasaduke[2] described four members of a family with Sorsby's dystrophy, all of whom developed bilateral macular hemorrhagic lesions in their third decade. Three eyes of two patients were treated. One eye received argon laser photocoagulation with no improvement in vision. Two eyes of the second patient also received photocoagulation, but the method was not described. In this patient, visual acuity in the right eye improved from 20/600 to 20/300; visual acuity in the left eye declined from 20/20 to 20/60. Carr, Noble, and Nasaduke[2] preferred the name hereditary hemorrhagic macular dystrophy and recommended early photocoagulation treatment to prevent legal blindness, which occurs frequently among affected patients.

We treated two brothers with hereditary hemorrhagic macular dystrophy, one treated by argon green laser photocoagulation and one by krypton red laser photocoagulation. We also studied the findings in other family members.

Case Reports

Case 1

A 28-year-old man had decreased vision for one week in the left eye. Diabetes mellitus, diagnosed two years previously, was controlled with 20 units of lente insulin daily.

Best-corrected visual acuity was R.E.: 20/20 (+0.50 −0.50 × 115) and L.E.: 20/70 (+0.50 −0.50 × 90). Intraocular pressure was 18 mm Hg in each eye. Results of slit-lamp examination in both eyes were similar. The cornea and lens were clear, the anterior chamber was deep without cells, pigment, or flare, but there were fine transillumination defects along the entire periphery of the iris.

Ophthalmoscopic examination disclosed a generalized, fine granularity of the retinal pigment epithelium that involved the posterior pole and fundus periphery of both eyes. Neither eye had any sign of diabetic retinopathy. The clinical appearance of the right macula was normal, but there was a pigment epithelial detachment temporal to the left fovea with an overlying serous detachment of the sensory retina. Fluorescein angiography confirmed the normal appearance of the right macula and demonstrated a neovascular membrane in the left eye with leakage 500 μm from the foveal avascular zone. The choroidal background fluo-

Accepted for publication Nov. 27, 1990.

From Retina Associates, and Eye Research Institute, Boston, Massachusetts. This study was supported in part by the Massachusetts Lions Eye Research Fund, Inc.

Reprint requests to Ronald C. Pruett, M.D., Eye Research Institute, 20 Staniford St., Boston, MA 02114.

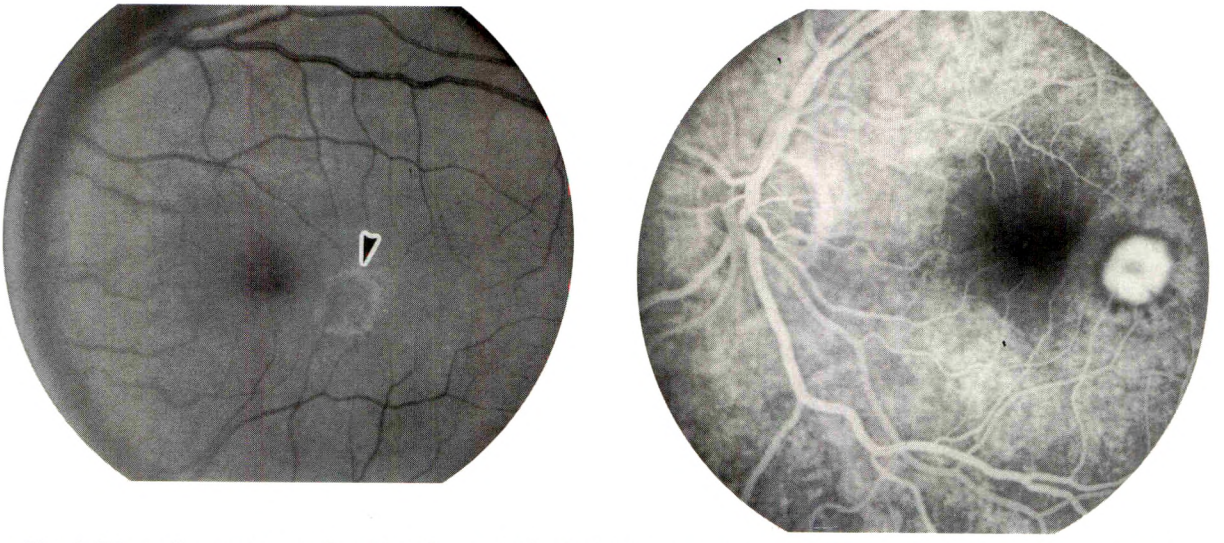


Fig. 1 (Wu and associates). Case 1, left eye. Left, Retinal pigment epithelial detachment (arrow) and shallow detachment of surrounding sensory retina. Right, Arteriovenous fluorescein angiogram showing leaking choroidal neovascular membrane temporal to fovea and generalized granularity of the retinal pigment epithelium.

rescence appeared mottled in both eyes because of irregularities of the pigment epithelium (Fig. 1).

Argon green laser photocoagulation (514.5 nm) was applied to the neovascular network of the left eye. One month later visual acuity remained at 20/70; six months after treatment it was 20/200. Fluorescein angiography showed a subfoveal recurrence of the neovascular membrane (Fig. 2), but the patient refused further treatment. Twelve years later visual acuity remained 20/200. A dry, pigmented macular scar was present that produced a 40-degree diameter, dense, central scotoma with a sharp border.

When first examined, the right macula was normal. Eight months later visual acuity had decreased to 20/70. A retinal pigment epithelial defect and a small subretinal hemorrhage were observed in the inferotemporal aspect of the fovea. Argon green laser photocoagulation was applied to a subretinal neovascular membrane detected by fluorescein angiography. During the subsequent 19 months, three additional argon green laser treatments were performed for recurrent neovascular growth (Fig. 3). Best-corrected visual acuity was 20/40. Nine years later visual acuity had decreased to 20/400 because of development of a dry, pigmented macular scar that produced a 40-degree central scotoma. Since then, the macular appearance and function have remained stable.

All laboratory testing was performed when the macular lesions were in the cicatricial stage. The electroretinogram was performed after 30 minutes of dark adaptation.[3] Under photopic conditions, the a-wave was 75% of normal amplitude in the right eye, and 57% of normal amplitude in the left eye (age-matched normal value, 280 to 326 μV). The b-wave amplitude was 91% of normal amplitude in both eyes (normal value, 336 to 516 μV). The lowest normal limit was used to calculate the percentage of normal values obtained during testing. The a-wave peak time was delayed in both eyes. The electro-oculogram light peak vs dark trough ratio was R.E.: 1.74 and L.E.: 1.61 (normal, greater than 1.8). A dark adaptation curve, measured on the left eye, was increased by 1 log unit. Farnsworth-Munsell D-15 color vision testing disclosed no abnormality.

Case 2

The 34-year-old brother of the patient described in Case 1 had a sudden decrease in vision of the left eye. He had myopia (R.E.: -4.75 -0.75×150; L.E.: -5.00 -1.00×50) and a two-year history of bilateral open-angle glaucoma treated with timolol maleate 0.5% and dipivefrin hydrochloride 0.1% twice daily.

Spectacle-corrected visual acuity was R.E.: 20/30 and L.E.: 20/100. Intraocular pressure by tonometry was R.E.: 24 mm Hg and L.E.: 22 mm Hg. There were subtle transillumination



Fig. 2 (Wu and associates). Case 1, left eye. Extensive submacular neovascularization six months after argon green laser treatment.

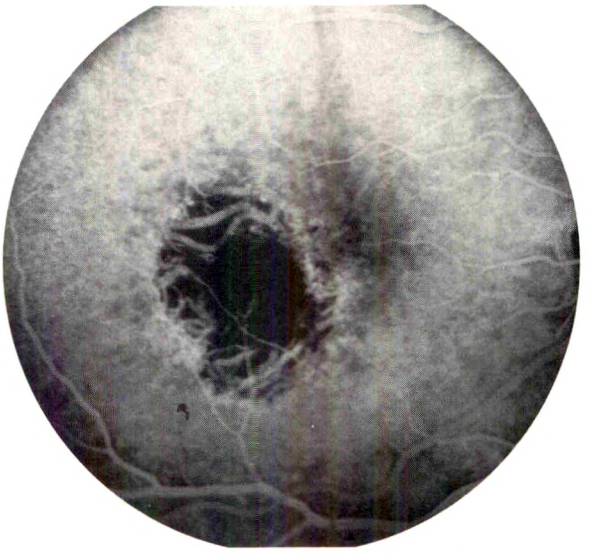


Fig. 3 (Wu and associates). Case 1, right eye. Fluorescein angiogram after four argon green laser treatment sessions with destruction of neovascular network.

defects along the pupillary margin and mid iris. Gonioscopy disclosed pigmentation of the trabecular meshwork in both eyes. The anterior segments were otherwise normal.

There was a small myopic crescent along the temporal border of each disk, both of which showed glaucomatous cupping (cup/disk ratio of 0.6) with preservation of the temporal neural rim. The fundi were blonde with fine granularity of the retinal pigment epithelium. Both maculae were abnormal. The right macula showed a pigment epithelial defect in the nasal region of the fovea; the left macula had a bleeding subretinal neovascular network nasal to the fovea that was confirmed by fluorescein angiography (Fig. 4).

Krypton red laser photocoagulation (647 to 676 nm) was applied to the macular neovascular network. At one week there were early pigmentary changes, the blood was reabsorbing, and visual acuity had improved to 20/40. To treat recurrent neovascular membranes, krypton red laser photocoagulation was delivered three months later and again four months later. More than one year after the third laser treatment, there was a dry, depigmented scar in the nasal aspect of the fovea that produced a 20 × 20-degree scotoma between the blind spot and fixation. Visual acuity was 20/50 after three years.

The pigment epithelial defect in the nasal portion of the right fovea showed bleeding two months after the initial examination (Fig. 5). Best-corrected visual acuity was 20/40. Angiographically demonstrated neovascularization in that region was treated with krypton red laser photocoagulation, and recurrences were treated five and six weeks later. Stable visual acuity of 20/100 was recorded almost three years after the last treatment. There was a dry, depigmented scar with a large, irregular scotoma measuring 20 degrees horizontally and 40 degrees vertically between the blind spot and fixation.

Electrophysiologic measurements performed 15 months apart were almost identical. The electroretinogram was performed after 30 minutes of dark adaptation. The a-wave amplitude was reduced to 69% of normal in the right eye and 77% of normal in the left eye (age-matched normal value, 371.6 to 451.6 μV). The b-wave amplitude was normal in both eyes. The electro-oculogram light peak vs dark trough ratio was R.E.: 2.05 and L.E.: 2.12 (normal, greater than 1.8). A dark adaptation curve of the left eye showed a slightly increased (1.5 log units) rod threshold. Color vision testing was not performed.

Other Family Members

Seventeen members in three generations of this family were examined. Historical information was obtained on 12 others among five generations (Fig. 6). The earliest family mem-

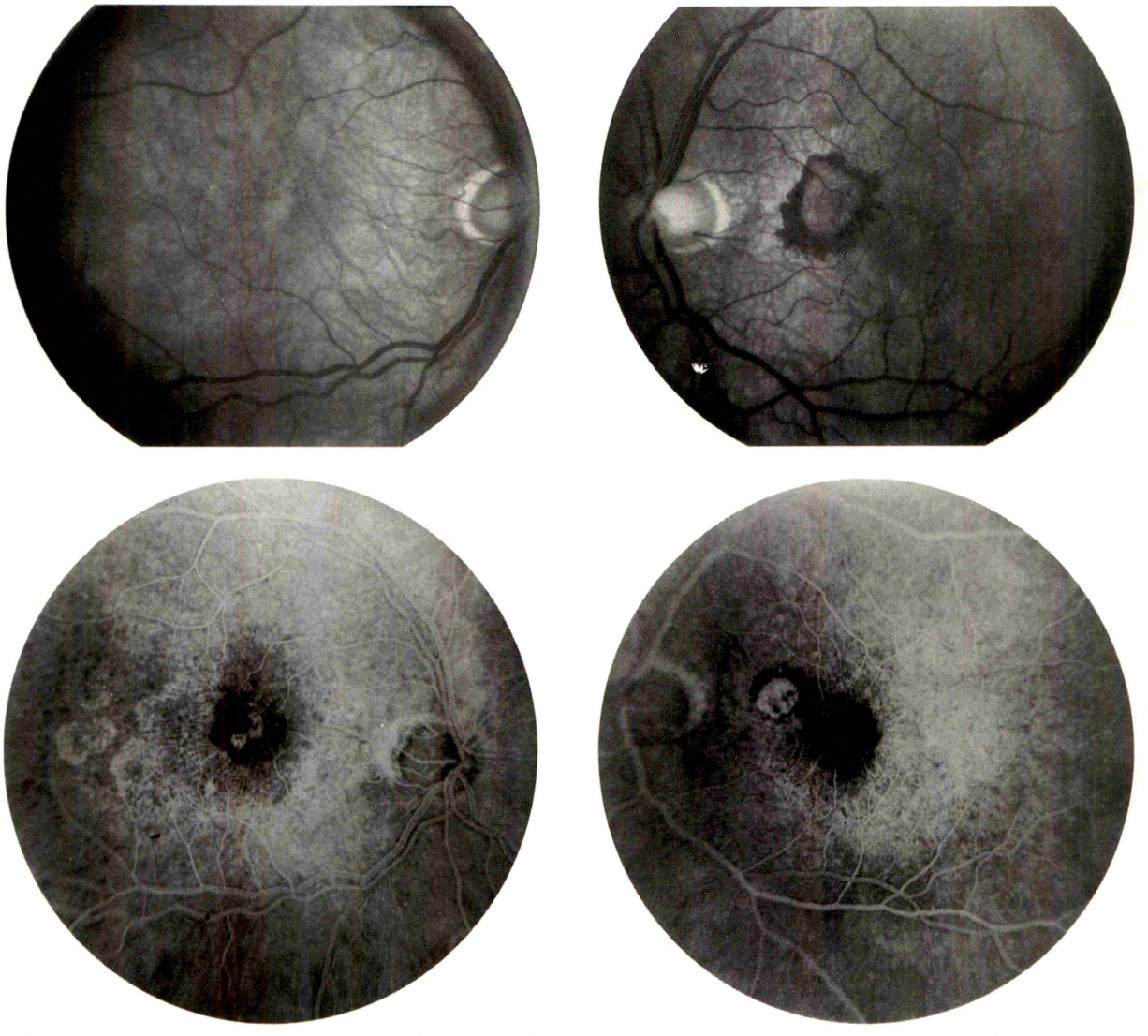


Fig. 4 (Wu and associates). Case 2. Top left, Faint pigment epithelial retinal defects in nasal fovea in right eye. Top right, Bleeding neovascular membrane nasal to fovea in left eye. Bottom left, Fluorescein angiogram done by referring ophthalmologist several days earlier demonstrating patchy retinal pigment epithelial defects in posterior pole with more focal windows in fovea in right eye. Bottom right, Similar patchy retinal pigment epithelial abnormality with nasal neovascular invasion in left eye.

ber believed to be affected was the paternal great grandfather (I-1) of the propositus (IV-2), who was reported to have both macular degeneration and glaucoma. He became blind as an adult. His daughter (II-1), paternal grandmother of the propositus, was similarly affected. One of her children (III-1) was the father of the propositus. He was 64 years of age when we examined him. He had noted slightly impaired vision at age 24 years. At age 26 years he was told he had bilateral chorioretinitis. He was forced to discontinue work as an accountant at age 30 years because of failing vision. Open-angle glaucoma was diagnosed at age 57 years. Bilateral filtering surgery had been performed, and he was using pilocarpine 4% four times daily and dipivefrin hydrochloride 0.1% twice daily in both eyes. His right fundus showed a macular lesion similar to that of the propositus, with extensive retinal pigment epithelial atrophy and pigmentary hyperplasia. The peripheral fundus also had fine mottling of the retinal

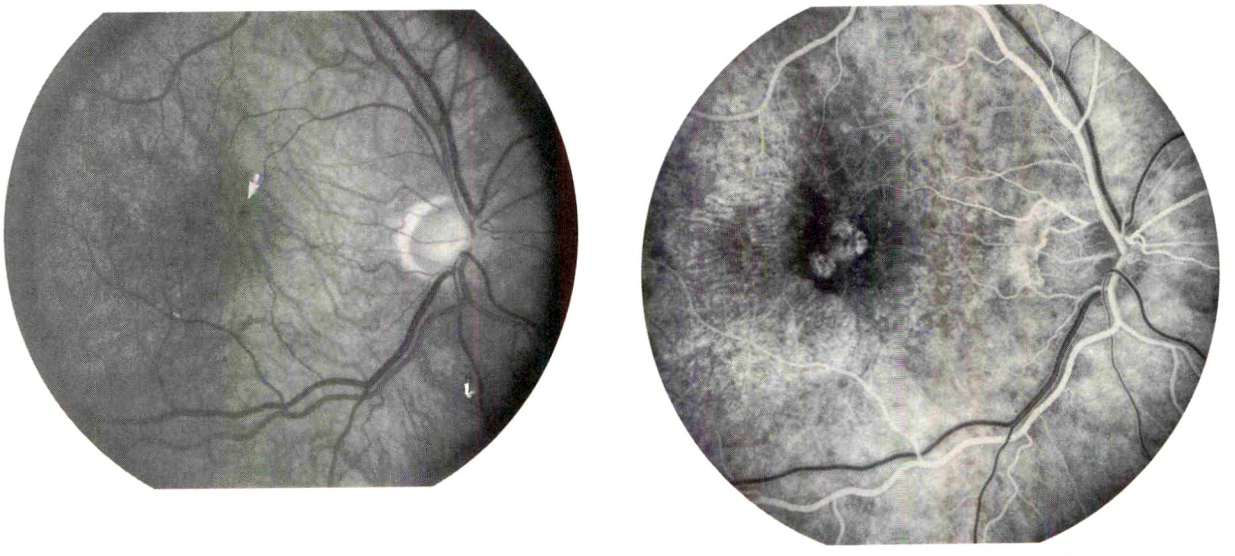


Fig. 5 (Wu and associates). Case 2, right eye. Left, Microhemorrhage (arrow) on nasal aspect of fovea. Right, Small neovascular tuft in that region shown by fluorescein angiography.

pigment epithelium but was unaffected by cicatricial changes. The left fundus could not be observed because of a dense cataract.

No paternal aunt, uncle, or first cousin of the propositus was known to have ocular disease. Two female cousins (IV-6, 7) were examined and had normal findings. Among the siblings of the propositus was his affected brother (IV-3), and two other brothers and a sister who had normal findings on examination. None of the next generation of this family appeared to be affected definitely. These children, three boys and five girls, ranged in age from 2 to 11 years. One, an 11-year-old girl (V-8), did show a fine granular appearance of the peripheral retinal pigment epithelium. She had pale fundi, light hair, and blue irides similar to her mother (IV-5), who had no detectable disease. Light pigmentation of hair, skin, and eyes was found in most members of this family.

The following laboratory studies were performed on relatives of the propositus and his brother, including some of the children in generation V: fluorescein angiography in five members; electroretinography and visual-evoked potential in 13; electro-oculography in seven; central and peripheral visual field measurement in eight; Farnsworth-Munsell D-15 color testing in ten; and flicker frequency profiles, dark adaptation testing, and serologic *Histoplasma* antibody screening in nine. No definite abnormalities were detected except on electroretinography testing. The father of the propositus (III-1) showed a bilateral overall reduction in electroretinography; he had bilateral macular lesions, advanced glaucoma, and cataract. One (IV-1) of the affected brothers had normal electrophysiologic testing results; another brother (IV-4) and the sister (IV-5) had slightly reduced photopic and scotopic b-waves on electroretinography and normal electro-oculogram values.

Discussion

We believe that these two brothers had the pseudoinflammatory macular dystrophy described by Sorsby, Joll Mason, and Gardener[1] and others.[2,4] Both brothers were affected by bilateral choroidal neovascular invasion of the macula, during their third and fourth decades of life, which evolved into a disciform scar with reduction of central vision. Their father and two earlier paternal progenitors also lost vision from what appeared to be a similar problem caused by an autosomal dominant hereditary defect. As found by Carr, Noble, and Nasaduke[2] in two patients, the electro-oculograms in our patients were within or close to normal limits, but we observed some decrease in electroretinogram responses in the two brothers and two of their siblings. These findings may distin-

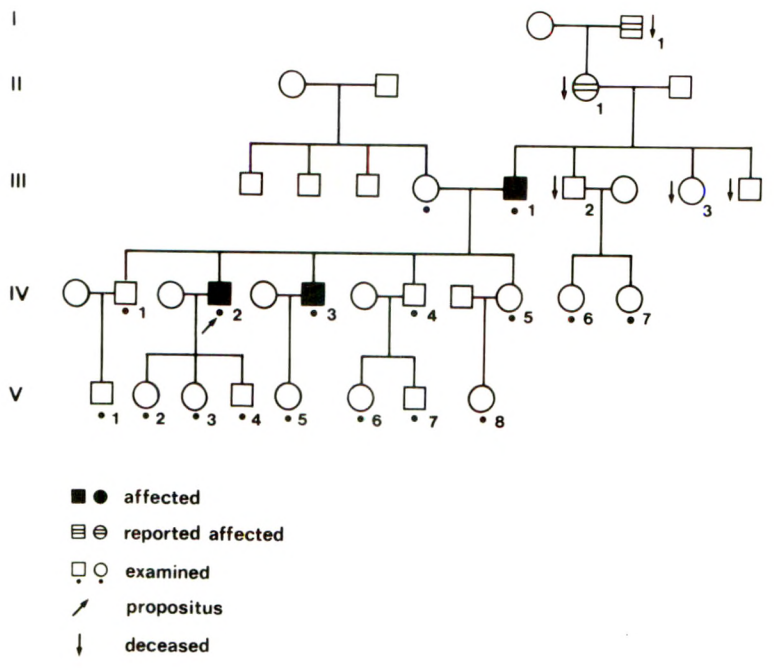


Fig. 6 (Wu and associates). Pedigree of family.

guish hereditary hemorrhagic macular dystrophy from a similar dominant macular dystrophy reported by Dreyer and Hidayat[5] in which both the electroretinogram and electro-oculogram were abnormal in the two patients described. We have not noted the drusen deposits at the level of Bruch's membrane, the angioid streaks, and the yellow plaque submacular material shown by Hoskin, Sehmi, and Bird[6] in their study of additional members of one of the original families reported by Sorsby, Joll Mason, and Gardener.[1] The iris pigment epithelial transillumination defects found in the two brothers may be related to the diabetes mellitus in one and the myopia and open-angle glaucoma with pigment dispersion in the other.

Evidence has been reported that there is considerable variation in the pigmentary pattern of

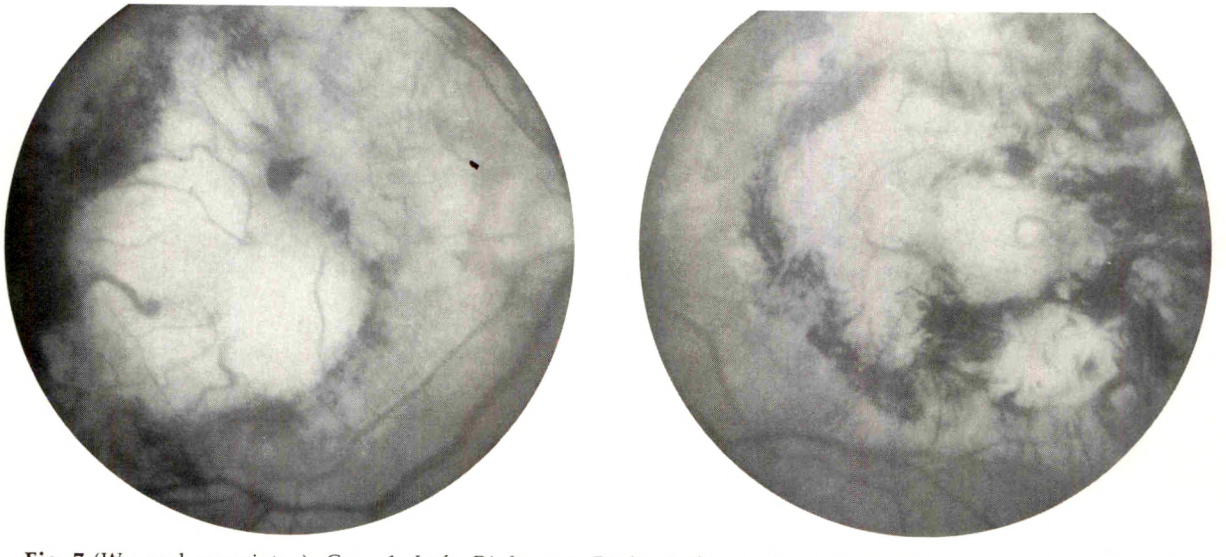


Fig. 7 (Wu and associates). Case 1. Left, Right eye. Right, Left eye. Long-term appearance of maculae after treatment with argon green laser photocoagulation showing large hypertrophic scars with pigment.



Fig. 8 (Wu and associates). Case 2. Left, Right eye. Right, Left eye. Both eyes were treated with krypton red laser photocoagulation and had flat atrophic scars without pigment.

the fundus and that there is a tendency for the atrophy of the retina, pigment epithelium, and choroid to progress slowly toward the periphery.[7] Yellow material, 30 μm in thickness, was demonstrated histologically within Bruch's membrane and stained positively for lipids.[8] Furthermore, this deposit has been judged responsible for delayed filling of the choriocapillaris during fluorescein angiography.[9] This was believed to be the earliest phenotypic marker of the disease,[9] but the same phenomenon was observed in 26% of eyes with age-related macular degeneration.[10] Although we had not recognized delayed choriocapillary filling at the time our patients were undergoing treatment, a review of their fluorescein angiograms indicated that they also demonstrated this sign.

Glaucoma was in the ocular history of two other members of this pedigree as well as in one family of the pedigree of Carr, Noble, and Nasaduke.[2] One member of the Carver family and one member of the Randall family in the study of Sorsby, Joll Mason, and Gardener[1] had glaucoma. Pigmentary changes were noted in the iris epithelium, and the trabecular meshwork of our patient was pigmented. Although glaucoma may be associated with this disorder, that aspect of the disease requires more study.

The pathophysiologic process of hereditary hemorrhagic macular dystrophy may not be fundamentally different from that of the age-related disciform lesion. Four eyes of two patients in the pedigrees of Sorsby, Joll Mason, and Gardener[1] were examined pathologically by Ashton and Sorsby[11] in 1951. Findings included dehiscences in Bruch's membrane, choroidal neovascularization of the subretinal space, and glial cicatrization of the outer retinal layers. Unfortunately the eyes were of older patients and dominant transmission of the defect was not established. The recorded natural progression of this disorder indicates that visual acuity can be expected to diminish to the level of legal blindness in both eyes of most affected patients. Hoskin, Sehmi, and Bird[6] indicated that the interval between visual loss from macular hemorrhage in the two eyes varied from nine months to ten years.

A review of the laser treatment of our patients permitted comparison of the effectiveness of argon green laser and krypton red laser photocoagulation in controlling neovascular invasion in genetically similar patients. If ultimate visual function is the best criterion, as measured by Snellen visual acuity and visual field testing, eyes treated with the red krypton laser fared better. Their final scarring was sharply defined, less hypertrophic, and smaller in area. But no final judgment can be made regarding wavelength because of other differences in the details of treatment. One patient (Case 1) treated with green argon laser photocoagulation, was less willing than his brother to return for frequent examinations, fluorescein angiography, and laser treatment. Also, green argon laser photocoagulation was delivered in 0.2-second pulses at 100- to 200-mW intensity, whereas red krypton laser photocoagulation was applied in 0.4-second pulses at 200 to 300 mW. Another factor that varied was the total

energy delivered during treatment of each eye: Case 1, green argon laser, L.E.: 4.18 J and R.E.: 28.21 J; Case 2, red krypton laser, L.E.: 19.42 J and R.E.: 15.90 J. Finally, red krypton laser was used for the patient in Case 2 after we had gained an additional ten years of experience with treatment of choroidal neovascular membranes (Figs. 7 and 8).

It is reasonable to conclude that laser treatment can be helpful in at least some patients with this syndrome.[2] Forsius and associates[12] described one patient who was treated with modest success. Although the patient's visual acuity was counting fingers before and after treatment, two years later visual acuity in one eye improved to 20/200. Hamilton and associates[7] had no success when treating seven eyes of four patients with argon or krypton laser photocoagulation; all had recurrences and became untreatable within two years. Visual acuity in our patient (Case 2), R.E.: 20/50 and L.E.: 20/100, allows him to function as a school teacher. His myopia may have been an initial advantage because submacular neovascular networks in eyes with higher degrees of myopia are less likely to progress.[13] The myopia may be a long-term disadvantage, however, because of the tendency of atrophic lesions in such eyes to enlarge with time. For this patient, and for his younger relatives, continuing close follow-up has been recommended.

References

1. Sorsby, A., Joll Mason, M. E., and Gardener, N.: A fundus dystrophy with unusual features. Br. J. Ophthalmol. 33:67, 1949.

2. Carr, R. E., Noble, K. G., and Nasaduke, I.: Hereditary hemorrhagic macular dystrophy. Am. J. Ophthalmol. 85:318, 1978.

3. Hirose, T., Wolf, E., and Hara, A.: Electrophysiological and psychophysical studies in congenital retinoschisis of X-linked recessive inheritance. Doc. Ophthalmol. 13:173, 1977.

4. Burn, R. A.: Further cases of a fundus dystrophy with unusual features. Br. J. Ophthalmol. 34:394, 1950.

5. Dreyer, R. F., and Hidayat, A. A.: Pseudoinflammatory macular dystrophy. Am. J. Ophthalmol. 106:154, 1988.

6. Hoskin, A., Sehmi, K., and Bird, A. C.: Sorsby's pseudoinflammatory macular dystrophy. Br. J. Ophthalmol. 65:859, 1981.

7. Hamilton, W. K., Ewing, C. C., Ives, E. J., and Carruthers, J. D.: Sorsby's fundus dystrophy. Ophthalmology 96:1755, 1989.

8. Capon, M. R. C., Marshall, J., Krafft, J. I., Alexander, R. A., Hiscott, P. S., and Bird, A. C.: Sorsby's fundus dystrophy. Ophthalmology 96:1769, 1989.

9. Polkinghorne, P. J., Capon, M. R. C., Berninger, T., Lyness, A. L., Sehmi, K., and Bird, A. C.: Sorsby's fundus dystrophy. A clinical study. Ophthalmology 96:1763, 1989.

10. Pauleikhoff, D., Chen, J. C., Chisholm, I. H., and Bird, A. C.: Choroidal perfusion abnormality with age-related Bruch's membrane change. Am. J. Ophthalmol. 109:211, 1990.

11. Ashton, N., and Sorsby, A.: Fundus dystrophy with unusual features. A histological study. Br. J. Ophthalmol. 35:751, 1951.

12. Forsius, H. R., Eriksson, A. W., Suvanto, E. A., and Alanko, H. I.: Pseudoinflammatory fundus dystrophy with autosomal recessive inheritance. Am. J. Ophthalmol. 94:634, 1982.

13. Avila, M. P., Weiter, J. J., Jalkh, A. E., Trempe, C. L., Pruett, R. C., and Schepens, C. L.: Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology 91:1573, 1984.

A Simple Transposition Procedure for Complicated Strabismus

Edward G. Buckley, M.D., and Lois M. Townshend, M.D.

We combined a recession or resection of recti muscles with a vertical or horizontal transposition to correct a complicated paralytic ocular deviation in eight patients. The transposed muscles were reattached to the globe parallel to the spiral of Tillaux and adjacent to the paralyzed muscle. Postoperatively, seven patients demonstrated fusion in the primary position or required a slight head turn to fuse. There were no surgical complications, and no patient developed symptomatic cyclotropia, diplopia, or anterior segment ischemia.

CURRENT PROCEDURES to correct paralytic ocular deviations with combined horizontal and vertical components require detachment of three or four recti muscles from the globe, which significantly increases the risk of anterior segment ischemia.[1-4] Preexisting abnormalities may make bilateral procedures difficult, or it may be undesirable to operate on the unaffected fellow eye. Additionally, the secondary deviation may itself be so marked as to require surgery on three or four recti muscles to obtain adequate alignment. To correct such deviations, we combined a transposition of recti muscles with a recession and resection, which permitted correction of the full deviation with a minimum number of rectus muscle manipulations.

Accepted for publication Oct. 10, 1990; revised manuscript received Nov. 9, 1990.

From the Departments of Ophthalmology and Pediatrics, Duke University Medical Center, Durham, North Carolina.

Reprint requests to Edward G. Buckley, M.D., Department of Ophthalmology, Duke University Eye Center, Box 3802, Durham, NC 27710.

Patients and Methods

Between January 1985 and December 1988, eight patients underwent a combined transposition/recess/resect operation. Each patient was examined six months or longer after the operation. Five of the patients were female and three were male. Four of the patients were younger than 4 years of age. The patient in Case 2 had previous bimedial rectus muscle recessions and a right inferior oblique myectomy elsewhere. The motility and sensory examinations were performed by an orthoptist independent of the operating surgeon. Preoperative and postoperative examination of each patient included a complete ocular examination combined with ocular motility measurements by the prism and cover test at far and at near and in the major fields of gaze.

The sensory status was evaluated by the Bagolini striated lenses (far and near), the Worth four-dot (far and near), and the Randot stereogram. Preexisting amblyopia in children was treated with patching until visual acuity in each eye was equal. Postoperative examination also included an assessment of any abnormal head position required to attain fusion. Cyclotropia was measured in adults using the double Maddox rod test. Limitations of ductions were scored on a scale from −1 to −4, with −4 representing complete lack of function.

Each patient had a complicated strabismus that involved a severe weakness of one or more of the extraocular muscles combined with a secondary deviation (Table 1). In each patient, the transposition direction was chosen to improve the weakest ocular rotation. Four of the patients had only the combined transposition/recess/resect operation, and four patients required additional rectus muscle procedures (Table 1).

We modified the standard full tendon transposition procedure[4] by reattaching the rectus muscle end to the globe parallel to the spiral of Tillaux instead of perpendicular to the muscle margin. This is the same method used when supra- or infraplacing a muscle for an A or V pattern, except that the transposed muscle is moved all the way to the margin of the adjacent paralytic muscle. The transposed muscles were then recessed or resected in relationship to the spiral of Tillaux (Fig. 1).

We made a conjunctival peritectomy at the corneoscleral limbus, and the rectus muscle was isolated with a Jamison muscle hook. The check ligaments were severed. If the muscle was to be recessed, a 6-0 double-armed Vicryl suture was woven through the tendon of the muscle and secured with a double-locking knot at the muscle margin on each side. The muscle was then disinserted by using Wescott scissors, transposed to the new position adjacent to the muscle margin, and sutured to the globe parallel to the spiral of Tillaux. The muscle was recessed from the insertion of the paralyzed muscle.

For resection, a 6-0 double-armed Vicryl suture was woven through the muscle at the desired resection area, a small hemostat was clamped anterior to the suture line, and the muscle was cut anterior to the clamp. The residual stump was excised. The muscle was then transposed to the new position and sutured to the globe adjacent to the insertion of the paralytic rectus muscle and parallel to the spiral of Tillaux. The conjunctiva was closed with an 8-0 Vicryl suture.

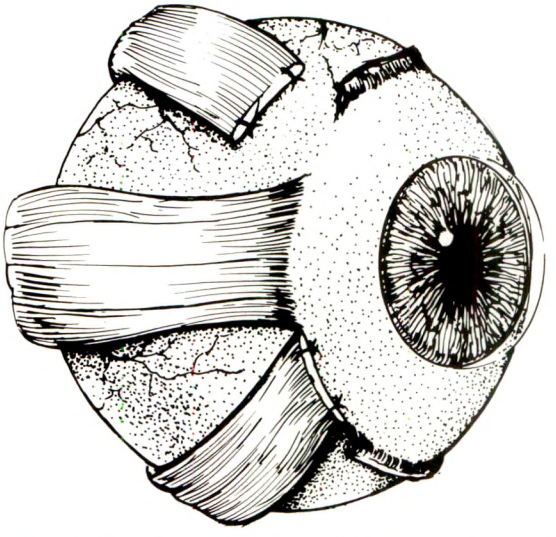


Fig. 1 (Buckley and Townshend). A combined transposition/recess/resect procedure for a sixth nerve palsy and hypertropia. The superior rectus muscle is transposed laterally and recessed along the superior border of the lateral rectus muscle with the insertion parallel to the spiral of Tillaux. The recession amount is measured from the lateral rectus muscle insertion. The inferior rectus muscle is resected and transposed laterally with the superior border attached to the inferior border of the lateral rectus muscle.

Results

All patients had significant improvement in their ocular motility (Table 2). One of the patients (Case 3) is shown in Figures 2, 3, and 4. Seven patients demonstrated fusion with the Worth four-dot either in the primary position or with a slight head turn. Three patients had fusion with the Worth four-dot both at far and at near in the primary position. One patient lowered her chin to permit fusion and stereopsis. Three patients, all children, developed a slight head position in which the eyes were orthophoric using the prism cover test. The patient in Case 2 had a normal head position but was too young to give reliable results on sensory testing.

Cyclotropia was measured using the double Maddox rod test on four patients (Cases 1, 3, 4, and 5). Each had a cyclodeviation of less than 5 degrees, and none had cyclodiplopia. There were no surgical complications, and no patient developed anterior segment ischemia.

Discussion

In 1921, O'Connor[5] recommended complete disinsertion and full rectus muscle transposition for the treatment of paralytic strabismus. In 1959, Schillinger[6] described a full muscle transposition procedure for the treatment of abducent nerve palsy in which the superior and inferior recti muscles were sutured midway between their original insertions and the lateral rectus muscle insertion and parallel to the spiral of Tillaux. This procedure is similar to the one we used, except we performed a resection and recession on the transposed muscles and

TABLE 1
PREOPERATIVE MEASUREMENTS AND SURGICAL PROCEDURE*

CASE NO., AGE (YRS), SEX	DIAGNOSIS	20 FEET	13 INCH	LEFT	RIGHT	UP	DOWN	DUCTIONS
1, 28, F	Left oculomotor nerve partial palsy	16 XT 10 RHT	16 XT 10 RHT	16 RHT	40 XT 8 RHT	40 RHT	25 XT 20 LHT	−4 left superior rectus −3 left medial rectus −2 left inferior rectus −2 left inferior oblique
2, 2, F	Left oculomotor nerve partial palsy	45 XT 60 RHT	45 XT 60 RHT	45 XT 45 RHT	90 XT 60 RHT	45 XT 50 RHT	45 XT 45 RHT	−3 left medial rectus −2 left inferior rectus −3 left inferior oblique −4 left superior rectus
3, 18, F	Bilateral oculomotor nerve palsy	90 XT 20 LHT	90 XT 20 LHT	60 XT 25 LHT	80 XT 10 LHT	70 XT 20 LHT	55 XT 20 LHT	−2 left medial rectus −4 left inferior rectus −2 right inferior rectus −1 both superior recti
4, 2, F	Bilateral abducens nerve, right oculomotor nerve partial palsy	75 ET 50 LHT	90 ET 40 LHT	90 ET 40 LHT	90 ET 40 LHT	90 ET 60 LHT	90 ET 15 LHT	−3 right lateral rectus −2 left lateral rectus −4 right superior rectus −2 right inferior oblique
5, 3, M	Left oculomotor nerve and left trochlear nerve palsy	30 XT 20 RHT	45 XT 30 RHT	45 XT 35 RHT	30 XT 30 RHT	45 XT 45 RHT	45 XT 20 LHT	−4 left superior rectus −2 left medial rectus −2 left inferior rectus −2 left inferior oblique
6, 22, M	Left blowout fracture	35 LHT 15 XT	35 LHT 16 XT	20 LHT 10 XT	35 LHT	15 RHT	35 LHT 8 XT	−4 left inferior rectus
7, 16, F	Right double elevator palsy	20 ET 30 LHT	35 ET 50 LHT	14 ET 35 LHT	20 ET 50 LHT	40 ET 50 LHT	25 ET 35 LHT	−4 right inferior oblique −4 right superior rectus
8, 3, M	Left hypertropia, right abducens nerve	50 ET 20 LHT	45 ET 20 LHT	45 ET 30 LHT	60 ET 20 LHT	30 ET 15 LHT	45 ET 10 LHT	−4 right lateral rectus −1 right superior rectus

*XT = exotropia; LHT = left hypertropia; ET = esotropia; and RHT = right hypertropia.

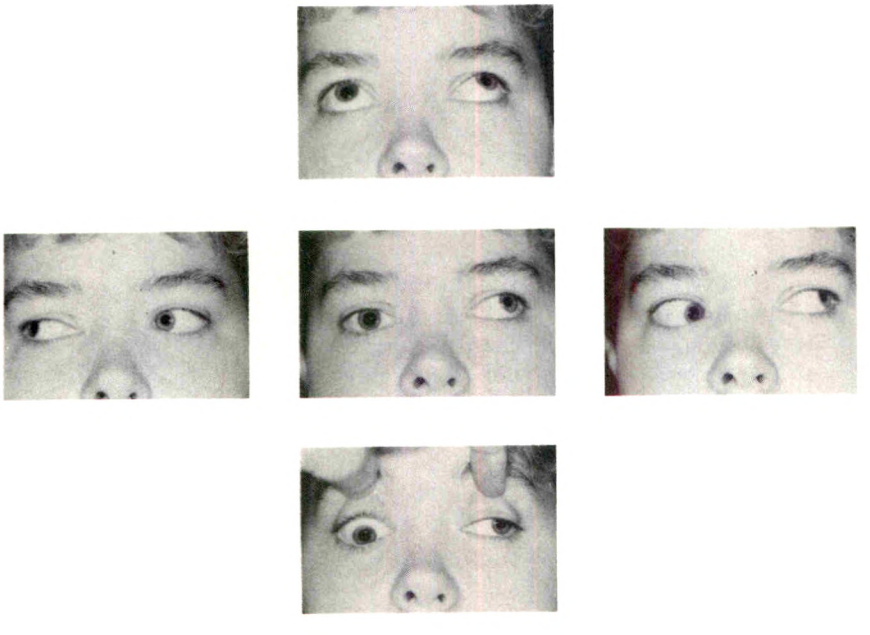


Fig. 2 (Buckley and Townshend). Case 3. Preoperative appearance showing large-angle exotropia and left hypertropia. Note the marked limitation of depression in the left eye.

TABLE 1 *(Continued)*

SURGERY
Left medial rectus resection 4 mm, left lateral rectus recession 6 mm, and transposition of both up
Left lateral rectus recession 8 mm, left medial rectus resection 6 mm, and transposition of both up; right lateral rectus recession 10 mm; right superior rectus recession 6 mm
Left medial rectus resection 6 mm, left lateral rectus recession 10 mm, and transposition of both down; right medial rectus resection 6 mm; right lateral recession 10 mm
Right lateral rectus resection 8 mm, right medial rectus recession 6 mm, and transposition of both up; left medial rectus recession 6 mm; left lateral rectus resection 8 mm
Left medial rectus resection 6 mm, left lateral rectus recession 8 mm, and transposition of both up
Left medial rectus resection 4 mm, left lateral rectus recession 5 mm, and transposition of both down Right medial rectus recession 5 mm, right lateral rectus resection 6 mm, and transposition of both up; right inferior rectus recession 5 mm Right superior rectus resection 6 mm, right inferior rectus recession 5 mm, and transposition of both laterally

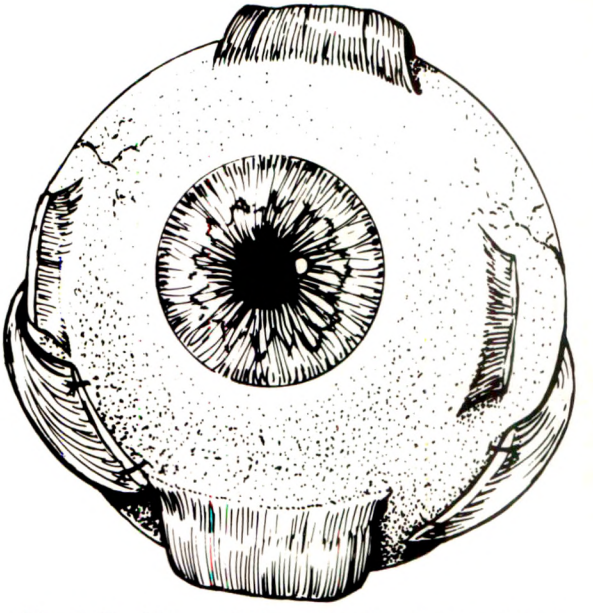


Fig. 3 (Buckley and Townshend). Case 3. Medial rectus muscle is resected and transposed inferiorly; lateral rectus muscle is transposed inferiorly and recessed.

sutured the muscles adjacent to the margin of the paralytic muscle. The recession and resection adds little difficulty to the transposition procedure and does not require significant additional tissue manipulation. A technique similar to ours has been used with some success (Stewart Wolfe, M.D., oral communication, August 1990).

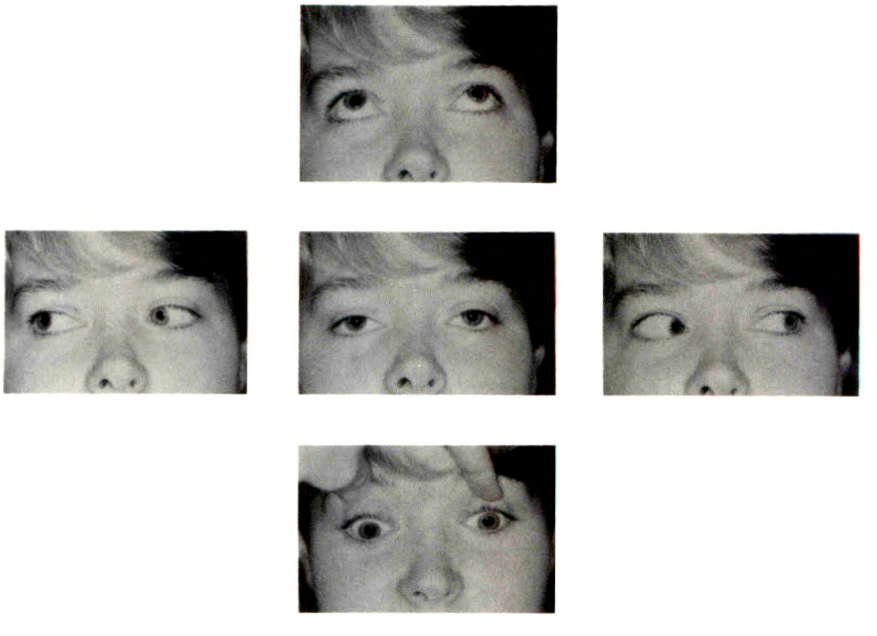


Fig. 4 (Buckley and Townshend). Case 3. Thirty-six months postoperatively, the patient is orthophoric in primary position. Note improved depression of left eye.

TABLE 2
POSTOPERATIVE RESULTS

CASE NO.	20 FEET	13 INCH	LEFT	RIGHT	UP	DOWN	SENSORY	HEAD POSITION	FOLLOW-UP (MOS)
1	Orthophoria	Orthophoria	10 ET	10 X(T) 8 LH(T)	14 RHT	12 XT 10 LHT	Fusion, 800 sec	Normal	36
2	12 X(T) 10 LH(T)	12 X 8 LH	10 XT 10 RHT	20 XT 15 RHT	10 X(T) 5 RH(T)	15 X(T) 8 RH(T)	Too young	Chin tuck	10
3	12 X 4 LH	20 X	8 RH(T)	10 ET 8 LHT	8 X(T)	8 X(T)	Fusion, 400 sec	Normal	36
4	10 X(T) 10 LH(T)	10 X(T) 8 LH(T)	5 E(T) 5 LH(T)	5 XT 5 LHT	30 XT 10 LHT	10 X(T) 10 RH(T)	Too young	Chin elevation	10
5	10 ET 8 LHT	10 ET 10 LHT	20 ET 10 RHT	10 ET	20 ET 10 RHT	10 XT 10 LHT	Too young	Left turn	12
6	6 LH(T)	4 LH(T)	10 LHT	6 LH(T)	Orthophoria	10 LH(T)	Fusion, 100 sec	Chin tuck	6
7	Orthophoria	10 E	Orthophoria	12 LHT 12 ET	12 LHT 12 ET	Orthophoria	Fusion	Normal	6
8	3 X(T)	3 X(T)	10 XT	12 ET	4 ET 8 LHT	6 X(T)	Too young	Normal	30

X = exophoria; E = esophoria; ET = esotropia; XT = exotropia; RHT = right hypertropia; LH = left hyperphoria; LHT = left hypertropia; and (T) = intermittent occurrence.

The ocular motility disturbances in our eight patients constitute a group of abnormalities difficult to correct with previous techniques. Three patients had oculomotor nerve palsy; two patients had combined cranial nerve palsy; one patient had an abducent nerve palsy; one patient had double elevator palsy; and one patient had an orbital blowout fracture. These types of strabismus cases, with combined horizontal and vertical deviations and marked duction limitations, have always created significant therapeutic problems.

We were impressed by the amount of total deviation corrected using this procedure. Four patients (Cases 1, 5, 6, and 8) had only the transposition/recession/resection procedure. In each of these patients, we obtained significant improvement in their ocular alignment by operating on only two recti muscles. We were not able to limit the procedure to only two muscles in all patients by using this technique; however, we were able to operate on a smaller number of muscles and still correct large deviations associated with marked duction limitations. Four patients (Cases 2, 3, 4, and 7) all had such large preoperative deviations that, at the time of the combined procedure, additional rectus muscle surgery was required. This usually involved a standard recession and resection of the muscles of the contralateral eye.

We were concerned that a cyclodeviation may be induced by recessing and resecting the recti muscles in the transposed locations. This did not occur, because no patient had a cyclodeviation measuring greater than 5 degrees, and no patient had cyclodiplopia.

References

1. Saunders, R. A., and Phillips, M. S.: Anterior segment ischemia after three rectus muscle surgery. Ophthalmology 95:533, 1988.

2. McNeer, K. W.: Three complications of strabismus surgery. Ann. Ophthalmol. 7:441, 1965.

3. Saunders, R. A., and Sandall, G. S.: Anterior segment ischemia syndrome following rectus muscle transposition. Am. J. Ophthalmol. 93:34, 1982.

4. Helveston, E. M.: Muscle transposition procedures. Surv. Ophthalmol. 16:92, 1971.

5. O'Connor, R.: Transplantation of ocular muscles. Am. J. Ophthalmol. 4:838, 1921.

6. Schillinger, R. J.: A new type of tendon transplant operation for abducens paralysis. J. Int. Coll. Surg. 31:593, 1959.

Incidence of Prominent Corneal Nerves in Multiple Endocrine Neoplasia Type 2A

Shigeru Kinoshita, M.D., Fumi Tanaka, M.D., Yuichi Ohashi, M.D., Masataka Ikeda, M.D., and Shin-ichiro Takai, M.D.

We studied the increased visibility of corneal nerves inside an 8-mm diameter central corneal area in 14 patients with multiple endocrine neoplasia type 2A, one patient with multiple endocrine neoplasia type 2B, five patients with nonhereditary medullary thyroid carcinoma, ten patients with anterior keratoconus, and ten normal subjects. We used a grading system (grade 0 through grade 4) for nerve visibility based on slit-lamp biomicroscopic examination and photographic documentation. All 20 normal eyes showed either grade 0 or grade 1, which indicated no pathologic thickening of corneal nerves. Sixteen of the 28 eyes (57%) with multiple endocrine neoplasia type 2A, however, were evaluated as grade 2 or higher, which indicated thickened corneal nerves. The incidence of high nerve visibility in eyes with multiple endocrine neoplasia type 2A was significantly greater compared to normal eyes ($P < .0001$), anterior keratoconus ($P < .0001$), and nonhereditary medullary thyroid carcinoma ($P = .0012$). Furthermore, eight of the 28 eyes (29%) with multiple endocrine neoplasia type 2A showed markedly prominent corneal nerves (grade 3 and 4), a prominence similar to those seen in eyes with multiple endocrine neoplasia type 2B. There was no definite relationship among prominent nerve, age of the patient, and occurrence of pheochromocytoma. These findings suggest that over half of all patients with multiple endocrine neoplasia type 2A show corneal nerves pathologically thickened to different degrees.

In normal eyes, corneal nerves are not thick enough to visualize by slit-lamp biomicroscope, partly because of the absence of myelinated fibers.[1] Increased visibility of corneal nerves, however, is recognized in some ocular and systemic diseases. Secondary thickening of corneal nerves caused by nerve regeneration or regional inflammation can be seen in corneal diseases such as anterior keratoconus, Fuchs' corneal dystrophy, and failed graft.[2,3] The visibility itself, however, is mild and localized. Conversely, prominent corneal nerves over the entire cornea are thought to be associated with systemic diseases such as multiple endocrine neoplasia, neurofibromatosis, and leprosy.[4] Among these, it is generally accepted that multiple endocrine neoplasia type 2B consistently shows the most prominent corneal nerve in both corneas.[3,4]

Multiple endocrine neoplasia type 2A, also called Sipple's disease,[5] has several clinical characteristics similar to multiple endocrine neoplasia type 2B. For instance, both disorders accompany medullary thyroid carcinoma, high levels of plasma calcitonin, pheochromocytoma with autosomal dominant inheritance, or a combination of these. Additionally, multiple endocrine neoplasia type 2B is associated with marfanoid habitus, skeletal abnormality, thickened lips and eyelids, and neuroma of the intestine and tongue.[6,7] Moreover, several reports describe accompanying ocular manifestations of multiple endocrine neoplasia type 2B, such as prominent corneal nerves, conjunctival neuroma, and ocular dryness.[8,9] The relation-

Accepted for publication Dec. 4, 1990.

From the Departments of Ophthalmology (Drs. Kinoshita, Tanaka, and Ohashi), Surgery (Drs. Ikeda and Takai), and Clinical Genetics, Biomedical Research Center (Dr. Takai), Osaka University Medical School, Osaka, Japan. This study was supported in part by grants-in-aid for scientific research (02454406) and for cancer research (02151028 and 02152071) from the Ministry of Education, Culture, and Science of Japan, a grant from Osaka Eye Bank, Osaka, Japan, and the intramural research fund of Osaka University.

Reprint requests to Shigeru Kinoshita, M.D., Department of Ophthalmology, Osaka University Medical School, 1-1-50 Fukushima, Fukushimaku, Osaka 553, Japan.

ship of corneal nerve thickening in eyes with multiple endocrine neoplasia type 2A is important in consideration of the genetic difference between multiple endocrine neoplasia type 2A and multiple endocrine neoplasia type 2B, as well as the basic mechanism of corneal nerve thickening in multiple endocrine neoplasia type 2 syndrome.

Using our grading system of corneal nerve thickening, we studied corneal nerve visibility in patients with multiple endocrine neoplasia type 2A and compared the results with those from patients with multiple endocrine neoplasia type 2B, nonhereditary medullary thyroid carcinoma, anterior keratoconus, and normal subjects.

Patients and Methods

We studied 28 eyes of 14 Japanese patients with multiple endocrine neoplasia type 2A, including nine kindreds. All patients were treated by one of us (S.T.) between April 1990 and July 1990. Informed consent was obtained from the patients. Of these 14 patients with multiple endocrine neoplasia type 2A, nine showed both medullary thyroid carcinoma and pheochromocytoma, and five had medullary thyroid carcinoma with contributory family history of multiple endocrine neoplasia type 2A. Two patients had parathyroid adenopathy. None of the patients showed either marfanoid habitus, skeletal abnormality, thickened lips, thickened eyelids, or mucosal neuromas. Because of this, multiple endocrine neoplasia type 2A was diagnosed in these 14 patients as differentiated from multiple endocrine neoplasia type 2B.

We also examined two eyes of a patient with multiple endocrine neoplasia type 2B who had medullary thyroid carcinoma, pheochromocytoma, marfanoid habitus, skeletal abnormality, thickened lips and eyelids, and mucosal neuromas, ten eyes of five patients with nonhereditary medullary thyroid carcinoma unrelated to multiple endocrine neoplasia syndrome, 20 eyes of ten patients with anterior keratoconus, and 20 eyes of ten normal subjects.

For these patients and normal subjects, two corneal specialists performed slit-lamp biomicroscopic examination with a ×12-magnified objective lens. Detailed photographic documentation by scleral scattering (×10 objective lens) and slit-image (×25 objective lens) pictures were also performed by a slit-lamp microscope with an automatic exposure system. Corneal nerve visibility in an 8-mm diameter central corneal area was then evaluated separately by the two examiners (S.K. and F.T.) using our grading system (grade 0 to 4): grade 0, nerves are not visible by slit-lamp examination or any photographs; grade 1, fine nerves visible by slit-lamp examination but not by any photographs; grade 2, fine nerves visible by both slit-lamp examination and slit-image (×25) photographs but not scleral scattering (×10); grade 3, nerves visible by both slit-lamp examination, slit-image, and scleral scattering photographs; and grade 4, prominent nerves visible by all three methods (Figure). Although this clinical observation itself was not done in masked or random fashion, the final photographic evaluation was performed in masked fashion. Using this grading system, the two examiners gave different grades to three of the 78 eyes, in which cases we chose the lower grades.

Mann-Whitney U-test was used for statistical analysis when comparing the ranked nonparametric data from each group. Corneal sensitivity measurement by Cochet-Bonnet esthesiometer was also performed in all eyes.

Results

Of 20 normal eyes, 16 were evaluated as grade 0, which indicated no visible corneal nerves. The other four eyes were evaluated as grade 1, with corneal nerves faintly visible by slit-lamp examination. None of the eyes of the normal subjects were evaluated as higher than grade 2. Of the 28 eyes with multiple endocrine neoplasia type 2A, however, 16 (57%) were evaluated as grade 2 or higher, which indicated pathologically thickened corneal nerves. The incidence of high nerve visibility in eyes with multiple endocrine neoplasia type 2A was significantly greater compared to normal eyes ($P < .0001$), anterior keratoconus ($P < .0001$), and nonhereditary medullary thyroid carcinoma ($P = .0012$). Furthermore, eight of the 28 eyes (29%) with multiple endocrine neoplasia type 2A showed markedly prominent corneal nerves (grades 3 and 4), a prominence similar to that seen in eyes with multiple endocrine neoplasia type 2B (Table 1). All eyes with multiple endocrine neoplasia type 2A showed bilaterally similar grades of corneal nerve thickness, although

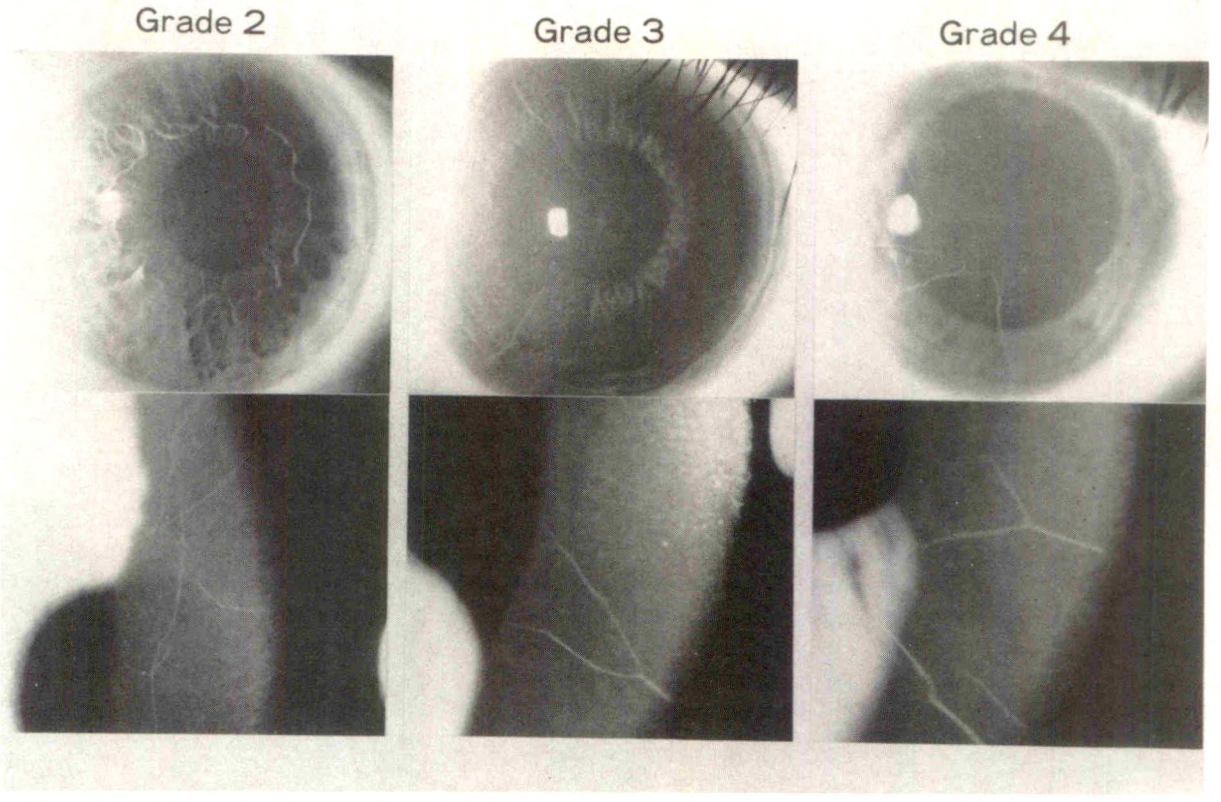


Figure (Kinoshita and associates). Grading system using photographic documentation. Grade 2, Fine nerve bundles are seen in the central cornea by slit-lamp (× 25) but not by scleral scattering (× 10) (multiple endocrine neoplasia type 2A). Grade 3, Several nerves are visible in the central cornea by both slit-lamp (× 25) and scleral scattering (× 10) (multiple endocrine neoplasia type 2A). Grade 4, Prominent nerve bundles are easily seen by both slit-lamp (× 25) and scleral scattering (× 10) (multiple endocrine neoplasia type 2B).

individual variability was observed (Table 2). There was no definite relationship between prominent nerve, age, and occurrence of pheochromocytoma.

In eyes with multiple endocrine neoplasia type 2A, slit-lamp biomicroscopic examination disclosed no neuroma in the limbal or conjunctival regions. The Cochet-Bonnet esthesiometer

TABLE 1
CORNEAL NERVE VISIBILITY

DISEASE	NO. OF EYES EXAMINED	GRADE OF CORNEAL NERVE VISIBILITY									
		0		1		2		3		4	
		NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)	NO.	(%)
Multiple endocrine neoplasia type 2A	28	3	(11)	9	(32)	8	(29)	7	(25)	1	(3)
Multiple endocrine neoplasia type 2B	2	—		—		—		—		2	(100)
Normal subjects	20	16	(80)	4	(20)	—		—		—	
Keratoconus	20	15	(75)	4	(20)	1	(5)	—		—	
Nonhereditary medullary thyroid carcinoma	8	5	(63)	3	(37)	—		—		—	

TABLE 2
CORNEAL NERVE VISIBILITY IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A

CASE NO., AGE (YRS), SEX	NERVE VISIBILITY* R.E.	NERVE VISIBILITY* L.E.	GENERAL MANIFESTATIONS: MEDULLARY THYROID CARCINOMA	PHEOCHROMOCYTOMA	PARATHYROID ADENOPATHY	NEUROMA	FAMILY HISTORY
1, 36, M	4	3	Yes	Yes	No	No	Yes
2, 28, F	3	3	Yes	No	No	No	Yes
3, 52, F	3	3	Yes	Yes	Yes	No	Yes
4, 26, M	3	2	Yes	Yes	No	No	Yes
5, 21, F	2	3	Yes	No	No	No	Yes
6, 53, F	2	2	Yes	No	No	No	Yes
7, 75, M	2	2	Yes	Yes	Yes	No	Yes
8, 44, F	2	1	Yes	Yes	No	No	Yes
9, 33, M	2	1	Yes	Yes	No	No	Yes
10, 57, F	1	1	Yes	Yes	No	No	Yes
11, 42, F	1	1	Yes	No	No	No	Yes
12, 27, F	1	0	Yes	Yes	No	No	Yes
13, 42, M	1	0	Yes	No	No	No	Yes
14, 71, M	0	1	Yes	Yes	No	No	Yes

*Nerve visibility was expressed using our grading system.

showed more than 40 mm in length in all eyes, which indicated corneal sensitivity within the normal range.

Discussion

If fibrillary opacities in the transparent corneal stroma are not only linear but also thicker in the periphery than in the center, reaching the limbal-corneal junction, they are most likely corneal nerves.[1,3] By observing these opacities in the central cornea by slit-lamp biomicroscope and photographic observation, we were able to document the degree of corneal nerve visibility. We concluded that the corneal nerve visibility up to grade 1 was within the normal range. Using this grading system, 19 of 20 eyes (95%) with anterior keratoconus, thought to show occasionally fibrillary nerves because of the ectasia,[2] showed grade 0 or grade 1. Only one eye with anterior keratoconus was evaluated as grade 2.

By contrast, we found that 16 of 28 eyes (57%) with multiple endocrine neoplasia type 2A showed grade 2 or higher, which indicated apparent corneal nerve visibility. Furthermore, eight of these eyes (29%) had extremely prominent nerves, a condition commonly seen in eyes with multiple endocrine neoplasia type 2B. This observation is contrary to previous reports that prominent corneal nerves are rarely seen in this disease.[9,10] This discrepancy may be partly caused by the corneal nerve visibility evaluation criteria. Robertson, Sizemore, and Gordon[9] used strict criteria, and it is likely that only the eyes similar to multiple endocrine neoplasia type 2B (for example, grade 4) were considered to show prominent corneal nerves. Since the corneal nerves of grades 2 and 3 (mostly seen in eyes with multiple endocrine neoplasia type 2A) were markedly distinguishable from those in normal eyes, although less prominent than those in multiple endocrine neoplasia type 2B, the corneal nerves in multiple endocrine neoplasia type 2A are likely to be of pathologic origin.

Multiple endocrine neoplasia type 2A has been reported to be linked to the genes near the centromere of chromosome 10.[11-13] Multiple endocrine neoplasia type 2B has also been reported to be linked closely to the same DNA markers to which multiple endocrine neoplasia type 2A has been linked,[14] although whether multiple endocrine neoplasia type 2A and multiple endocrine neoplasia type 2B are either allelic or part of a contiguous gene syndrome has not yet been determined. From the viewpoint of DNA linkage analysis, it is reasonable to speculate that the pathogenesis of corneal nerve thickening in multiple endocrine neoplasia type 2A is the same as or similar to that in multiple endocrine neoplasia type 2B, although the degree is different. Multiple endocrine neoplasia type 2A

may develop a milder form of corneal nerve thickening than multiple endocrine neoplasia type 2B. The clinical and basic significance of this concept is enormous. For instance, eyes of patients in the multiple endocrine neoplasia type 2A kindred who do not show clinical manifestations of multiple endocrine neoplasia type 2A should be examined at an early age, as in multiple endocrine neoplasia type 2B kindred.

Spector, Klintworth, and Wells[10] and Riley and Robertson[15] reported that corneal nerves observed in multiple endocrine neoplasia type 2B are prominent mainly because of the abundance of axons and Schwann cells, not of myelinated or abnormal extracellular substances. If so, at least two hypotheses regarding the pathogenesis of corneal nerve thickening in multiple endocrine neoplasia exist.

The first possibility is that in both multiple endocrine neoplasia type 2A and type 2B, a substance is secreted that stimulates the proliferation of Schwann cells or nerve growth. Medullary thyroid carcinoma, which secretes various polypeptide products such as calcitonin, corticotropin, prostaglandins, serotonin, and neuron-specific enolase,[7] is a possible source of secretion of such a substance. Patients with nonhereditary medullary thyroid carcinoma in our study, however, did not show any corneal nerve visibility, which implies that this carcinoma alone probably did not contribute to prominent nerve development. Pheochromocytoma was thought to be another candidate for a secreting site of such a substance,[16,17] although it was not widely accepted.[9] The second possibility is that numerous axons and Schwann cells are already located in the corneal stroma during corneal development. This is possible, since the organs involved in multiple endocrine neoplasia type 2 syndrome are thought to be of neural crest origin with gene abnormality.[18] Moreover, it has been reported that prominent corneal nerves can be seen in children with multiple endocrine neoplasia type 2B who are 3 or 4 years of age.

References

1. Hogan, M. J., Alvarado, J. A., and Weddell, J. E.: Histology of the Human Eye. Philadelphia, W. B. Saunders, 1971, p. 62.
2. Bron, A. J., Lobascher, D. J., Dixon, W. S., Das, S. N., and Ruben, M.: Fibrillary lines of the cornea. A clinical sign in keratoconus. Br. J. Ophthalmol. 59:136, 1975.
3. Mensher, J. H.: Corneal nerves. Surv. Ophthalmol. 19:1, 1974.
4. Grayson, M.: Diseases of the Cornea, ed. 2. St. Louis, C. V. Mosby, 1983, p. 466.
5. Sipple, J. H.: The association of pheochromocytoma with carcinoma of the thyroid gland. Am. J. Med. 31:163, 1961.
6. Decker, R. A., and Wells, S. A.: Multiple endocrine neoplasia. Jpn. J. Surg. 19:645, 1989.
7. Norton, J. A., and Wells, S. A.: Medullary thyroid carcinoma and multiple endocrine neoplasia type 2 syndromes. In Friesen, S. R., and Thompson, N. W. (eds.): Surgical Endocrinology, ed. 2. Philadelphia, J. B. Lippincott, 1990, p. 359.
8. Colombo, C. G., and Watson, A. G.: Ophthalmic manifestations of multiple endocrine neoplasia type three. Can. J. Ophthalmol. 11:290, 1976.
9. Robertson, D. M., Sizemore, G. W., and Gordon, H.: Thickened corneal nerves as a manifestation of multiple endocrine neoplasia. Trans. Am. Acad. Ophthalmol. Otolaryngol. 79:772, 1975.
10. Spector, B., Klintworth, G. K., and Wells, S. A., Jr.: Histologic study of the ocular lesions in multiple endocrine neoplasia syndrome Type II b. Am. J. Ophthalmol. 91:204, 1981.
11. Mathew, C. P., Chin, K. S., Easton, D. F., Thorpe, K., Carter, C., Liou, G. I., Fong, S. L., Bridges, C. B., Haak, H. H., Kruseman, A. C., Schifter, S., Hansen, H. H., Telenius, H., Telenius-Berg, M., and Ponder, B. A.: A linked genetic marker for multiple endocrine neoplasia type 2A on chromosome 10. Nature 328:527, 1987.
12. Simpson, N. E., Kidd, K. K., Goodfellow, P. J., McDermid, H., Myers, S., Kidd, J. R., Jackson, C. E., Duncan, A. M., Farrer, L. A., Brasch, K., Castiglione, C., Genel, M., Gertner, J., Greenberg, C. R., Gusella, J. F., Holden, J. J., and White, B. N.: Assignment of multiple endocrine neoplasia type 2A to chromosome 10 by linkage. Nature 328:528, 1987.
13. Jackson, C. E., and Norum, R. A.: Genetic mechanism of neoplasia in MEN 2. Henry Ford Hosp. Med. J. 37:116, 1989.
14. Jackson, C. E., Norum, R. A., Lafreniere, R. G., O'Neal, L. W., Nikolai, T. F., Delaney, J. P., Sisson, J. C., Sobol, H., Lenoir, G. M., Ponder, B. A. J., and Willard, H. F.: Update on linkage on the multiple endocrine neoplasia type 2B gene (MEN 2B) to chromosome 10 markers linked to MEN 2A. Am. J. Hum. Genet. 47:A10, 1990.
15. Riley, F. C., Jr., and Robertson, D. M.: Ocular histopathology in multiple endocrine neoplasia type 2b. Am. J. Ophthalmol. 91:57, 1981.
16. Braley, A. E.: Medullated corneal nerves and plexiform neuroma associated with pheochromocytoma. Trans. Am. Ophthalmol. Soc. 52:189, 1954.
17. Baum, J. L., and Adler, M. E.: Pheochromocytoma, medullary thyroid carcinoma, multiple mucosal neuroma. Arch. Ophthalmol. 87:574, 1972.
18. Pearse, A. G.: The cytochemistry and ultrastructure of polypeptide hormone-producing cells of the APUD series and embryologic, physiologic and pathologic implications of the concept. J. Histochem. Cytochem. 17:303, 1969.

Paraproteinemic Corneal Deposits in Plasma Cell Myeloma

Klaus-Peter Steuhl, M.D., Marcus Knorr, M.D., Jens Martin Rohrbach, M.D., Walter Lisch, M.D., Edwin Kaiserling, M.D., and Hans-Jürgen Thiel, M.D.

We treated two patients who had IgG-kappa-light chain monoclonal gammopathy with partially crystalline and partially amorphic corneal deposits. Impairment of vision made keratoplasty necessary for each patient. Histologic examination of the corneal specimens showed deposits that stained positively for Masson's trichrome in all corneal cells. Immunohistochemical tests identified these deposits as IgG-kappa-light chain immunoglobulin fragments. Electron microscopy showed intracellular, rhomboid-shaped deposits enveloped by a membrane. The same deposits appeared in the conjunctival epithelium, within subconjunctival fibrocytes, and in the plasma cells of the bone marrow. Immunoelectrophoresis showed IgG-kappa-light chain fragments in the blood serum, the lacrimal film, and the aqueous humor. This suggests that the intracellular immunoglobulin fragments may have entered the corneal and conjunctival epithelium by way of the lacrimal film, the keratocytes by way of the corneoscleral limbus vasculature, and the endothelial cells from the aqueous humor.

MONOCLONAL GAMMOPATHY results from uncontrolled proliferation of a plasma cell clone, which produces an excess either of immunoglobulins or their heavy or light chain fragments. Diseases associated with excessive secretion of monoclonal paraproteins are either benign, with limited plasma cell growth, or malignant, with uncontrolled plasma cell growth. The malignant monoclonal gammopathies (more than half of these are plasmacytomas[1]) are characterized by continuous growth of the plasma cell clone, which results in an exponential increase of the monoclonal protein in the blood. This leads to anemia, failure of the immune system, hypercalcemia, soft tissue and skin tumors, altered blood rheologic tests, and renal failure,[2] and osteolytic bone lesions when the tumor manifests extramedullarily. The annual incidence of plasma cell neoplasms is estimated as three in a population of 100,000.[3,4] The circulating paraproteins are considered responsible for nonamyloid organ deposits.[2,5] Ocular sites of paraprotein deposits are the conjunctival, corneal, and lens epithelium, keratocytes, endothelial cells, plasma cell infiltration of the uvea with concomitant uveitis, cysts of the ciliary body, hyperviscosity-derived occlusion of the retinal vessels, and retinal hemorrhages.[6,7] We studied partially crystalline and partially amorphous corneal deposits in two patients with plasma cell myeloma and associated monoclonal gammopathy.

Accepted for publication Dec. 6, 1990.

From the University Eye Clinic Tübingen (Drs. Steuhl, Knorr, Rohrbach, Lisch, and Thiel), and Institute of Pathology (Dr. Kaiserling), University of Tübingen, Tübingen, Germany. This study was supported in part by a grant from Pharm-Allergan, Karlsruhe, Germany.

Reprint requests to K.-P. Steuhl, University Eye Clinic, Schleichstr. 12, D-7400 Tübingen, Germany.

Case Reports

Case 1

In 1973, plasmacytoma was diagnosed in a 50-year-old man on the basis of typical pronounced increase of IgG fraction with a high paraprotein increase (IgG, 2,897 mg/dl; normal, 800 to 1,800 mg/dl), decrease of IgA and IgM, and the increased number of atypical plasma cells in aspirated sternal bone marrow (approximately 25%; normal, 2%). Immunoelectrophoresis identified the paraprotein as L-chain kappa type. Laboratory test results for serum lipids, enzyme status, and electrolytes were all normal. The blood cell counts were normal, with a mild anemia (hemoglobin between 6.8 g/dl and 11.7 g/dl). The patient had two osteolytic skull lesions and a bilateral carpal canal syndrome as extramedullary manifes-

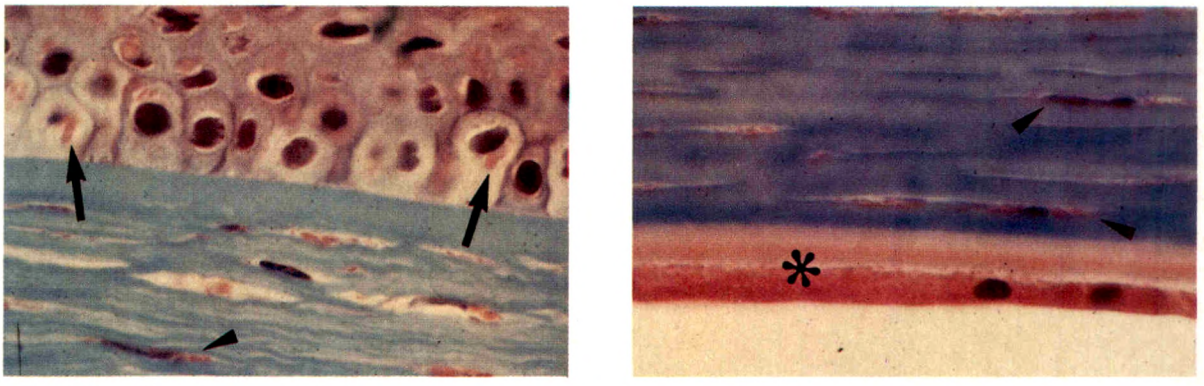


Fig. 1 (Steuhl and associates). Microscopic appearance of the superficial (left) and deeper (right) corneal tissue. Intracytoplasmic deposits within epithelial cells (arrows) and keratocytes (arrowheads). Note the endothelium filled with intracytoplasmic deposits and positive staining for Masson's trichrome (asterisk) (× 250).

tations of the disease. Repeated rectal biopsy specimens showed no signs of amyloidosis. Bence Jones proteinuria of approximately 300 mg/dl beginning in the early 1980s led to irreversible tubular damage and kidney atrophy. Dialysis was required in June 1985. Repeated treatment with 6 mg of melphalan daily for five days and 4 mg of methylprednisolone long-term resulted in no overall improvement. The patient died in August 1987.

A slight loss of corneal transparency without reduction in vision was observed in the early 1970s. When examined at the University Eye Clinic in Tübingen in April 1982, the corneas were hazy because of dense, white, partially crystalline deposits in all corneal layers, particularly the deep stroma and the endothelium. Apart from a nuclear cataract, other ophthalmic findings were unremarkable (the view of the fundus was obscured). There were no signs of active or recurrent uveitis. Penetrating keratoplasty was performed on the right eye in January 1984, and an extracapsular cataract extraction and posterior chamber intraocular lens implantation was performed in September 1984. Best-corrected visual acuity was 20/20. At that time, a slight, corneal haze was observed in the graft of the right eye. The opacities were located primarily in the deeper layers of the periphery of the transplant. In January 1985, visual acuity in the right eye was reduced to 10/20.

In April 1986, visual acuity in the left eye was 2/20. Simultaneous perforating keratoplasty and extracapsular cataract extraction with posterior chamber intraocular lens implantation was performed on the left eye, and best-corrected visual acuity was 8/20. In October 1986, corneal opacities had recurred in the left eye, and the transplant in the right eye showed deposits in all layers. Visual acuity was R.E.: 10/20 and L.E.: 6/20.

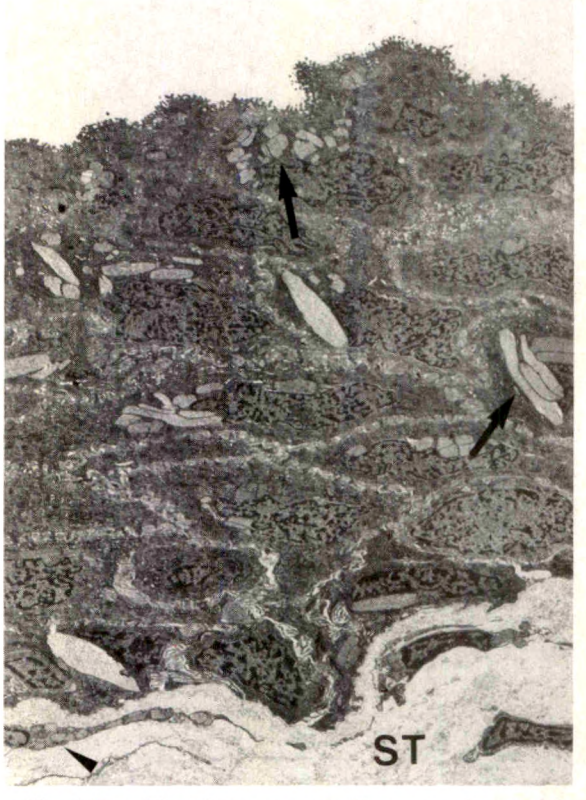


Fig. 2 (Steuhl and associates). Electron microscopic aspect of the conjunctival epithelium showing intracellular inclusions (arrows) and subepithelial tissue (ST). Note that the intracellular deposits are also visible within subepithelial fibrocytes (arrowhead) (× 1,600).

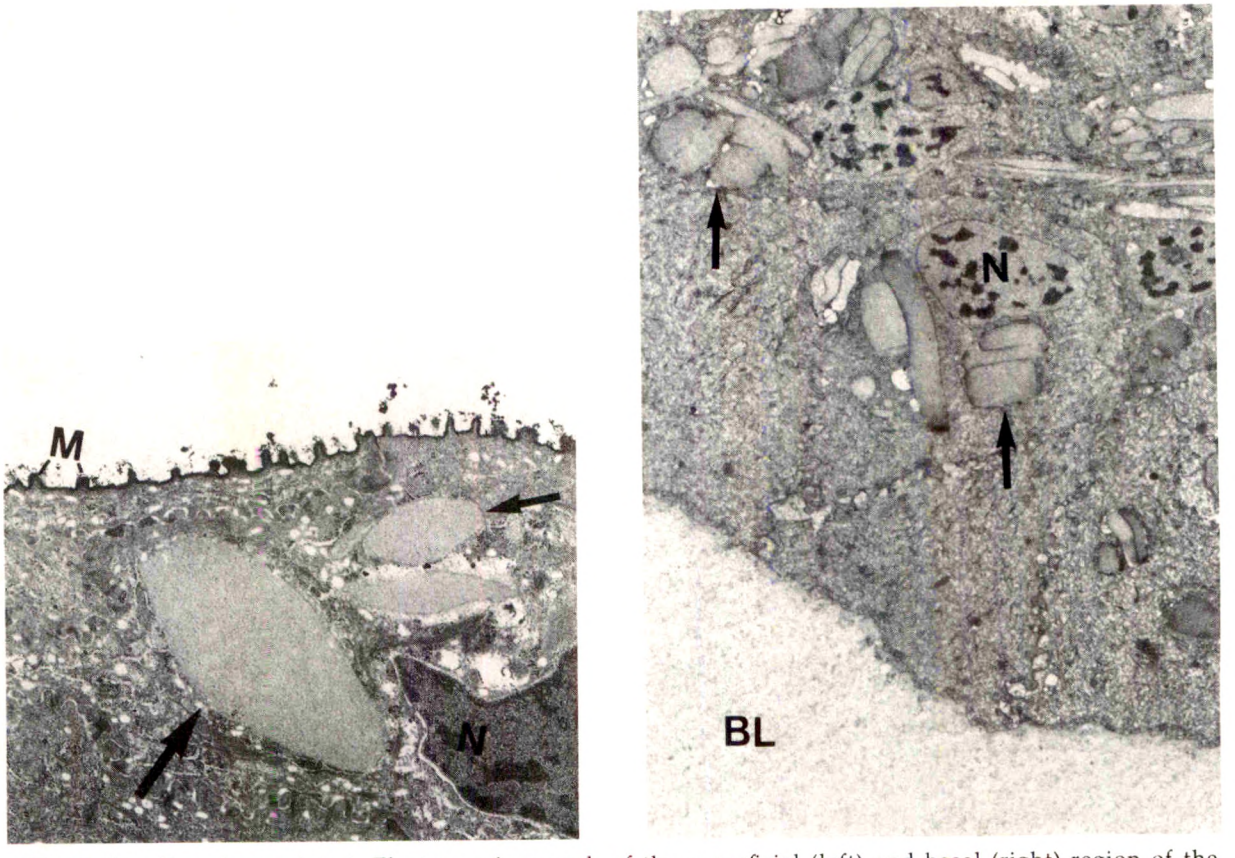


Fig. 3 (Steuhl and associates). Electron micrograph of the superficial (left) and basal (right) region of the corneal epithelium with numerous intracytoplasmic deposits (arrows). (M, microvilli; N, nuclei; and BL, Bowman's layer.) (Left, × 12,500; right, × 2,000.)

Case 2

In August 1989, plasmacytoma was diagnosed in a 78-year-old woman on the basis of typical findings in serum electrophoresis of IgG level greater than 4,000 mg/dl, decreased IgA level to 40 mg/dl, IgM level of 30 mg/dl, and bone marrow puncture with 18% plasma cells. Light microscopy showed that these plasma cells had marked vacuolization with crystalline inclusions. Immunoelectrophoresis showed a plasmacytoma of IgG-kappa-light chain type. Except for the ophthalmic findings, no extramedullary manifestations of the disease were found. Laboratory test results for serum lipids, enzyme status, and serum electrolytes (including calcium and copper) were normal. The patient had anemia (hemoglobin, 8.7 g/dl), and creatinine and urea levels were normal. The urine contained 150 mg/dl of protein (Bence Jones proteinuria of IgG-kappa-light chain type). Biopsy specimen of the oral mucosa showed no indication of generalized amyloidosis. The patient died Dec. 25, 1989, of pulmonary heart failure after cytostatic treatment of the disease.

The first myeloma-associated ocular involvement began in the late 1970s. In April 1988, visual acuity was R.E.: 3/20 and L.E.: 8/20. The reduced visual acuity was caused by diffuse, bilateral corneal haze. When examined at the University Eye Clinic Tübingen in September 1989, visual acuity was R.E.: 4/200 and L.E.: 6/20. Dense, diffuse, partially crystalline corneal opacities involved all corneal layers. In October 1989, perforating keratoplasty and extracapsular cataract extraction were performed in the right eye. There were no intraoperative or postoperative complications, and best-corrected visual acuity was 5/20.

Material and Methods

Semithin paraffin sections were stained with periodic acid-Schiff, Congo red, and Masson's

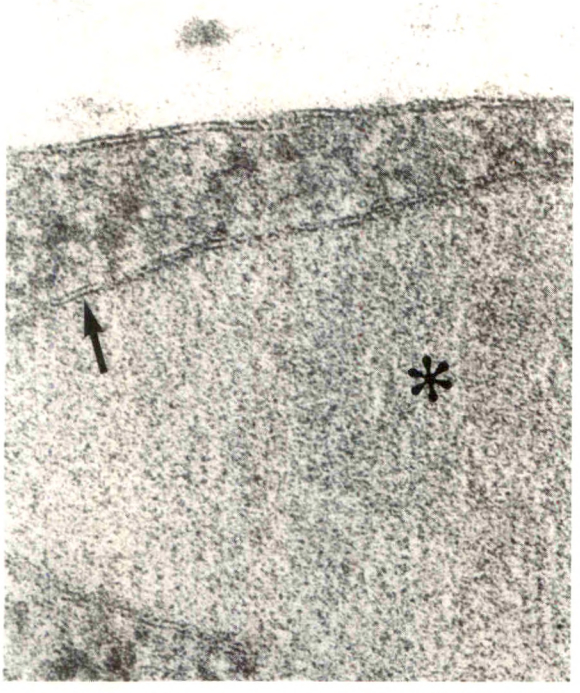


Fig. 4 (Steuhl and associates). Stromal keratocyte with typical intracytoplasmic inclusions (asterisk). These deposits are enveloped by a double membrane (arrow) and show a periodicity of approximately 16 nm (×75,000).

trichrome. Other sections were studied with the avidin-biotin peroxidase complex technique, using polyclonal rabbit antihuman antibodies to identify immunoglobulins or their fragments in corneal tissue. For transmission electron microscopy, the corneal specimens, conjunctiva, anterior lens capsule, and bone marrow of the iliac crest puncture were fixed in buffered glutaraldehyde solution, dehydrated, and embedded in Epon. Semithin sections were prepared with an ultramicrotome and stained according to Richardson, Jarett, and Finke's method.[8]

For immunoelectrophoretic determination of the immunoglobulins, tear fluid and aqueous humor specimens were taken intraoperatively with micropipettes. After electrophoretic splitting of the proteins, an immunofixation by monospecific anti-IgG and anti-kappa-light chain antisera was performed.[9]

Results

The corneal epithelium disclosed an intracytoplasmic edema primarily within the basal layer in both patients. The lamellae of the corneal stroma were loosened edematously, and the rarified endothelium disclosed vacuolic degeneration. In both cases intracytoplasmic deposits were located within all corneal cells and stained positive with Masson's trichrome (Fig. 1). Amyloid was excluded since they did not stain with Congo red and were negative for green birefringence. No extracellular material was found. Electron micrographs showed these intracytoplasmic deposits to be paracrystalline, rhomboid, and present in the conjunctival epithelium (Fig. 2), in the epithelial layers of the cornea (Fig. 3), in keratocytes (Fig. 4), and in the endothelial layer (Fig. 5), where they led to pronounced degenerative changes. This intracytoplasmic material was enveloped by a double membrane and had a periodicity of approximately 16 nm (Fig. 4). The same intercellular deposits were located within plasma cells of the iliac crest puncture by electron microscopy. As in light microscopy, no extracellular material was found.

Immunohistochemical analysis identified these corneal deposits as IgG-kappa-light chain immunoglobulin fragments (Fig. 6). They did not stain with anti-IgG, anti-IgM, anti-IgA, or anti-lambda-light chain antibodies, which indicated that these deposits corresponded to the paraproteins identified in the blood. IgG-kappa-light chain fragments were also found in the tears and the aqueous humor of one patient (Case 2) by immunoelectrophoresis (Fig. 7). The lens capsule and the lens epithelium had no deposits comparable to those of the corneal tissue.

Discussion

Plasma cell neoplasms consist of large numbers of plasma cells, representing one B-lymphocyte lineage. This cell population is descended from the original plasma cell and synthesizes homogeneous immunoglobulin or its fragments. Corneal accumulation of these components is uncommon in patients with multiple myeloma. No corneal deposits were found in 13 patients with multiple myeloma, and only one patient with primary amyloidosis had crystalline corneal deposits of 100 patients with monoclonal gammopathy.[10,11]

Intracellular and extracellular deposits were first described in 1917 in many organs of a patient with multiple myeloma and amyloido-

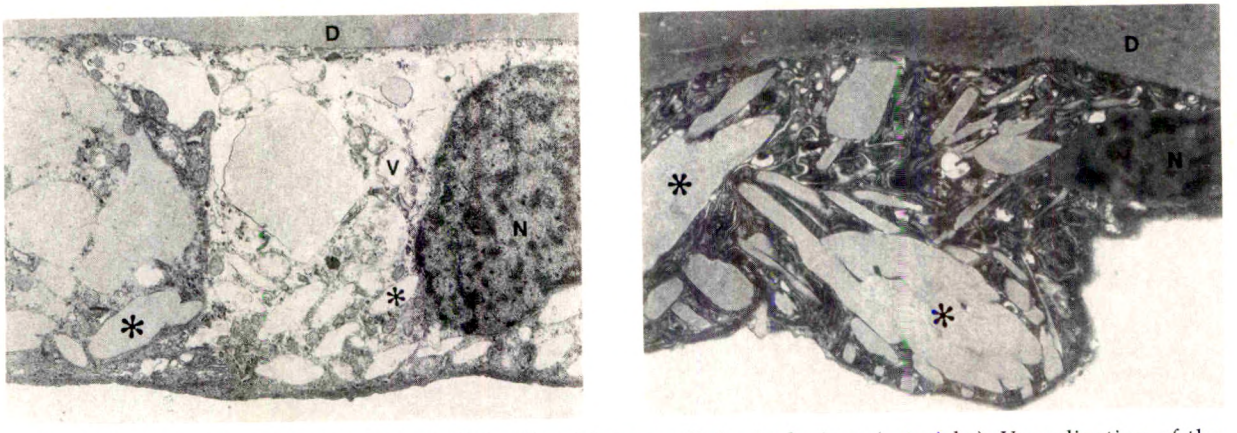


Fig. 5 (Steuhl and associates). Endothelial cells with intracellular inclusions (asterisks). Vacuolization of the cytoplasm (V) signals degenerative changes. (N, nucleus; and D, Descemet's membrane.) (Left, ×4,700; right, ×3,150.)

sis.[12] Corresponding corneal deposits first drew attention in 1934, when Meesmann[13] speculated that such crystalline corneal opacities involved the same deposits as the homogeneous or crystalline masses found in other organs of patients with myeloma. Aronson and Shaw[10] postulated that the corneal deposits were lipids. Conversely, François and Rabaey[14] and Pinkerton and Robertson[15] shared Meesmann's opinion. In 1978, Klintworth, Bredehoeft, and Reed[16] demonstrated immunohistochemically that the corneal deposits corresponded in all instances to the monoclonal protein of the causative plasma cell neoplasm. The rarity of such corneal changes in patients with plasma cell neoplasms is caused by two factors: a gammopathy of IgG-kappa-light chain type must be present, and the disease must be chronic. Characteristics of the paraproteins, such as solubility, the isoelectric point, susceptibility to proteolysis, the ability to interact specifically with cellular antigens and tissue, and other as yet unknown properties,[17,18] also play a part.

Paracrystalline corneal inclusions appear only when IgG-kappa-light chain proteins are synthesized by a proliferating monoclonal plasma cell.[19] Crystalline corneal deposits in IgG-lambda-light chain gammopathy, however, have been reported.[20,21] Both studies described the deposits as golden-brown and iridescent. Lewis, Falls, and Troyer[21] attributed the corneal opacities to an increase in serum copper level, with accompanying sunflower cataract. Firkin and associates[20] did not mention serum copper content.

Ormerod and associates[19] described intracellular and extracellular deposits in all corneal layers but were unable to verify this in the endothelium, since no endothelial cells were detectable in their preparation. All paracrystal-

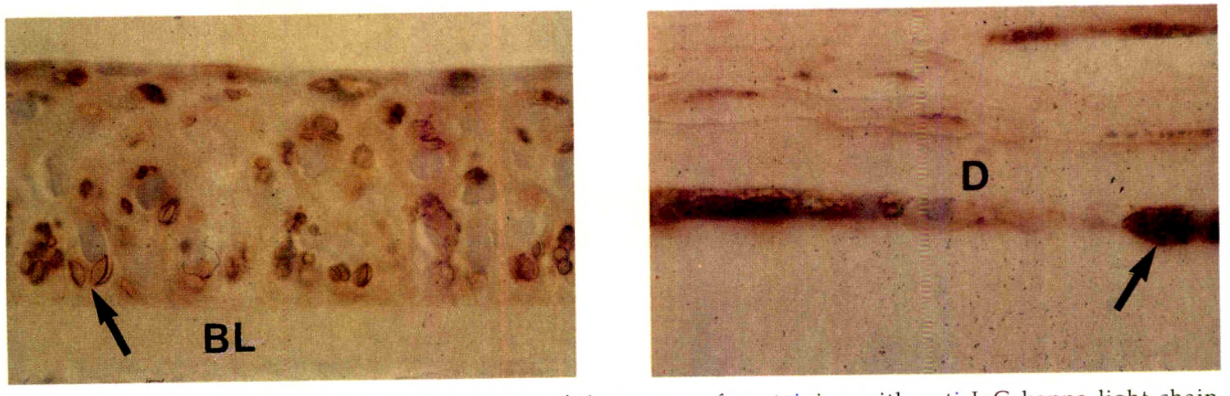


Fig. 6 (Steuhl and associates). Paraffin section of the cornea after staining with anti-IgG-kappa-light chain antibodies. The intracytoplasmic inclusions stained positively (arrows) (×250). (BL, Bowman's layer; and D, Descemet's membrane.)

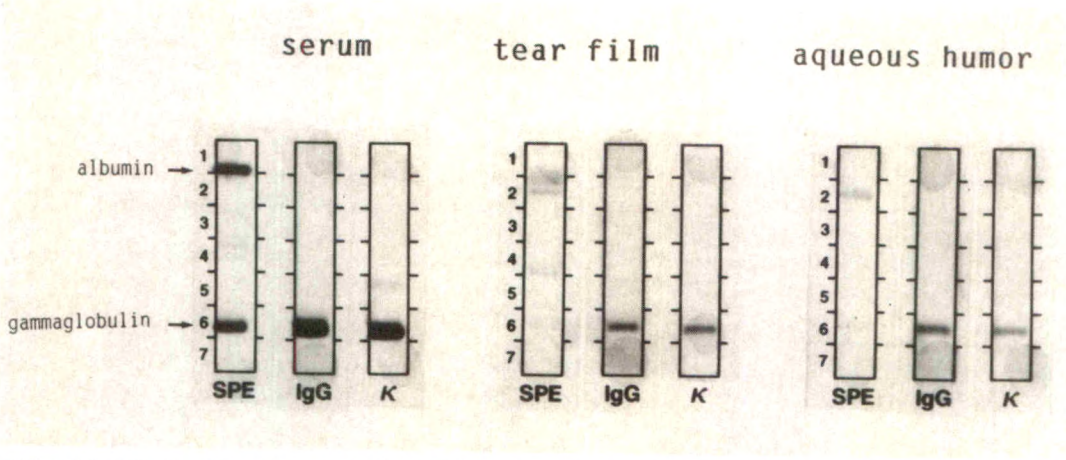


Fig. 7 (Steuhl and associates). Immunoelectrophoresis with clear IgG-kappa bands of the blood serum, the tear fluid, and the aqueous humor.

line deposits in the eyes of our patients were intracellular and present in both the superficial corneal epithelial cells and the conjunctival epithelium (Figs. 2 and 3).

Barr, Gelender, and Font[22] and Cherry and associates[23] also described exclusively intracellular paraprotein deposits. Barr, Gelender, and Font[22] regarded these as an indication that the protein inclusions develop from the corneal cells, but Cherry and associates[23] thought that the material was phagocytosed by the cells. We share the view of Cherry and associates, since the intracellular inclusions of our patients were surrounded by a double membrane (Fig. 4). The precipitation of the paraproteins is therefore probably associated with phagocytosis and the action of lysosomal enzymes.

In 1968, Gloor[24] noted that corneal changes in diseases that accompany paraproteinemia display a morphologic diversity. Different patterns of opacity have also been described regarding IgG-kappa-light chain type monoclonal gammopathy. Thus, anterior opacities may involve only the epithelium, Bowman's membrane, and the anterior stroma.[25,26] Lamellar keratoplasty is the preferred therapy if these opacities reduce vision markedly. Barr, Gelender, and Font[22] and Cherry and associates[23] described three cases in which partially crystalline and partially amorphous deposits involved the entire corneal stroma with no involvement of the epithelium or the endothelium. Furthermore, two cases have been reported in which deposits in the deep stroma left the corneoscleral limbus area clear.[14,27] The patients described by Ormerod and associates[19] and Meythaler and Flick[28] most resemble ours.

The factors that determine the extent and form of the deposits in IgG-kappa-light chain gammopathy have not been identified. The course, the intensity, and the duration of the disease may be important. Conversely, the location and form of the deposits may be influenced by the mechanisms by which paraproteins are transported to the corneal cells, the ability of the corneal cells to phagocytose, or by the biologic properties of the paraproteins.[17,18]

References

1. Ameis, A., Ko, H. S., and Pruzanski, W.: M-component. A review of 1244 cases. Can. Med. J. 114:889, 1976.

2. Bergsagel, D. E., and Rider, W. D.: Plasma cell neoplasms. In Devita, V. T., Hellman, S., and Rosenberg, S. A. (eds.): Cancer. Principles and Practice of Oncology. Philadelphia, J. B. Lippincott, 1985, p. 1753.

3. McMahon, B., and Clark, D. W.: Incidence of multiple myeloma. J. Chronic Dis. 4:508, 1956.

4. McPhedron, P., Heath, C. W., Jr., and Garcia, J.: Multiple myeloma incidence in metropolitan Atlanta, Georgia. Racial and seasonal variations. Blood 39:866, 1972.

5. Raman, S. B. K., and Van Slyck, E. J.: Nature of intracytoplasmic crystalline inclusions in myeloma cells. Am. J. Clin. Pathol. 80:244, 1983.

6. Ashton, N.: Ocular changes in multiple myelomatosis. Arch. Ophthalmol. 73:487, 1965.

7. Knapp, A. J., Gartner, S., and Henkind, P.: Multiple myeloma and its ocular manifestations. Surv. Ophthalmol. 31:343, 1987.

8. Richardson, K. C., Jarett, C., and Finke, E. H.:

Embedding in epoxy resins for ultrathin sectioning in electron microscopy. Stain Technol. 35:313, 1960.

9. Ritchie, R. F., and Smith, T. R.: Immunofixation. General principles and applications to agarose gel electrophoresis. Clin. Chem. 22:497, 1976.

10. Aronson, S. B., and Shaw, R.: Corneal crystals in multiple myeloma. Arch. Ophthalmol. 61:541, 1959.

11. Bourne, W. M., Kyle, R. A., Brubaker, R. F., and Greipp, P. R.: Incidence of corneal crystals in the monoclonal gammopathies. Am. J. Ophthalmol. 107:192, 1989.

12. Gaus, A.: Über multiples Myelozytom mit eigenartigen, zum Teil kristallähnlichen Zelleinlagerungen, kombiniert mit Elastolyse und ausgedehnter Amyloidose und Verkalkung. Virchows Arch. Pathol. Anat. 223:301, 1917.

13. Meesmann, A.: Über eine eigenartige Hornhautdegeneration (Ablagerung des Bence-Jonesschen Eiweißkörpers in der Hornhaut). Ber. Dtsch. Ophthalmol. Ges. 50:311, 1934.

14. François, J., and Rabaey, M.: Corneal dystrophy and paraproteinemia. Am. J. Ophthalmol. 52:895, 1961.

15. Pinkerton, R. M. H., and Robertson, D. M.: Corneal and conjunctival changes in dysproteinemia. Invest. Ophthalmol. Vis. Sci. 8:3157, 1969.

16. Klintworth, G. K., Bredehoeft, S. J., and Reed, J. W.: Analysis of corneal crystalline deposits in multiple myeloma. Am. J. Ophthalmol. 86:303, 1978.

17. Merlini, G., Farhangi, M., and Osserman, E. F.: Monoclonal immunoglobulins with antibody activity in myeloma, macroglobulinemia and related plasma cell dyscrasias. Semin. Oncol. 13:350, 1986.

18. Solomon, A.: Clinical implications of monoclonal light chains. Semin. Oncol. 13:3141, 1986.

19. Ormerod, L. D., Collin, H. B., Dohlman, C. H., Craft, J. C., Desforges, J. F., and Albert, D. M.: Paraproteinemic crystalline keratopathy. Ophthalmology 95:202, 1988.

20. Firkin, F. C., Lee, N., Ramsey, R., and Robertson, J.: Visual loss caused by corneal crystals in myeloma. Rapid improvement with plasma exchange and chemotherapy. Med. J. Aust. 29:677, 1979.

21. Lewis, R. A., Falls, F., and Troyer, D. O.: Ocular manifestations of hypercupremia associated with multiple myeloma. Arch. Ophthalmol. 93:1050, 1975.

22. Barr, C. C., Gelender, H., and Font, R. L.: Corneal crystalline deposits associated with dysproteinemia. Arch. Ophthalmol. 98:884, 1980.

23. Cherry, P. M. H., Kraft, S., McGowan, H., Ghosh, M., and Shenken, E.: Corneal and conjunctival deposits in monoclonal gammopathy. Can. J. Ophthalmol. 18:142, 1983.

24. Gloor, B.: Diffuse Hornhautdegeneration bei einem Fall von Makroglobulinämie Waldenström. Ophthalmologica 155:449, 1968.

25. Eiferman, R. A., and Rodrigues, M. M.: Unusual superficial stromal deposits in IgG kappa monoclonal gammopathy. Arch. Ophthalmol. 98:78, 1980.

26. Kremer, J., Wright, P., Merin, S., Weiss, J., Pick, A., and Kaufman, H.: Corneal subepithelial monoclonal kappa IgG deposits in essential cryoglobulinaemia. Br. J. Ophthalmol. 73:669, 1989.

27. Rodrigues, M. M., Krachmer, J. H., Miller, S. D., and Newsome, D. A.: Posterior corneal crystalline deposits in benign monoclonal gammopathy. Arch. Ophthalmol. 97:124, 1979.

28. Meythaler, H., and Flick, K.: Augenbeteiligung beim Plasmozytom. Klin. Monatsbl. Augenheilkd. 169:100, 1976.

Postoperative Complications After Molteno Implant Surgery

Shlomo Melamed, M.D., Michael Cahane, M.D., Isaac Gutman, M.D., and Michael Blumenthal, M.D.

We performed Molteno implant surgery in one eye each of 41 patients with uncontrolled glaucoma. Intraocular pressure was controlled (intraocular pressure less than or equal to 18 mm Hg) in 32 eyes (78%). The mean preoperative intraocular pressure was 40 ± 13.2 mm Hg, whereas the mean postoperative intraocular pressure was 16 ± 6.6 mm Hg. Patients were followed up for an average of 16 months after the operation. Visual acuity was unchanged in 23 eyes (56%), improved in nine eyes (22%), and poorer in nine eyes (22%). The major complications included shallow anterior chamber and hypotony in six eyes (14.6%), vitreous hemorrhage in two eyes (4.9%), retinal detachment in one eye (2.4%), and malignant glaucoma in two eyes (4.9%). Less grave complications included hyphema in four eyes (9.8%), peripheral choroidal effusion in 15 eyes (36.6%), obstruction of the tube in six eyes (14.6%), recession of the tube into the angle in two eyes (4.9%), erosion of the tube in one eye (2.4%), and Tenon's cyst formation in three eyes (7.3%).

THE MOLTENO IMPLANT is an aqueous drainage device designed to drain the aqueous from the anterior chamber through a tube into a reservoir located at the ocular equator. Various drainage devices are available,[1,2] but the Molteno implant has the most widespread clinical use.[3-12]

Although Molteno implant surgery is successful in controlling intraocular pressure in many eyes with refractory glaucoma, postoperative complications are common. These include erosion of the implant through the sclera or conjunctiva,[10,12] prolonged hypotony with obliteration of the anterior chamber, apposition of the tube to the corneal endothelium, which may lead to corneal edema, and obstruction of the tube with iris tissue vitreous gel, fibrin, or blood.[1,2,12,13] Other complications include choroidal effusion, suprachoroidal hemorrhage, retinal detachment, band keratopathy, pupillary block glaucoma, infection, and endophthalmitis.[1,10-12,14] Anterior chamber flattening and hypotony, one of the most hazardous complications, have been reported to occur less frequently after temporary ligation of the tube, two-stage operations, or after using a donor scleral patch graft.[4,7,10,12,15-18]

Postoperative complications of Molteno implant surgery are also affected by the advanced disease processes that usually exist in these eyes, such as inflammation, scarred conjunctiva, and neovascularization. We performed Molteno implant surgery in 41 patients with refractory glaucoma.

Patients and Methods

All patients had refractory glaucoma and had required either a filtering operation or cyclocryotherapy before Molteno implant surgery. Ocular examinations were performed in all patients, including best-corrected visual acuity, intraocular pressure measurements preoperatively and at intervals postoperatively, biomicroscopy, ophthalmoscopy, and visual field analysis. All patients underwent the same surgical procedure of one-stage single-plate Molteno implant surgery, performed by the same surgeon (S.M.) with retrobulbar anesthesia.

A fornix-based conjunctival flap was dissected at the superonasal or superotemporal quadrant with relaxing incisions of the conjunctiva to expose the sclera posterior to the equator. The Molteno plate was then secured to the sclera with 8-0 silk sutures, approximately 10.0 mm posterior to the corneoscleral limbus.

An anterior chamber paracentesis was fol-

Accepted for publication Aug. 6, 1990; revised manuscript received Dec. 17, 1990.

From the Department of Ophthalmology, Goldschleger Eye Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel.

Reprint requests to Shlomo Melamed, M.D., Goldschleger Eye Institute, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

lowed by injection of hyaluronic acid into the anterior chamber with a 30-gauge cannula. An 8.0 × 6.0-mm rectangular donor scleral patch graft was sutured to the sclera adjacent to the corneoscleral limbus with 9-0 nylon sutures at the anterior and posterior corners on one side. The scleral patch was reflected, and a 9-0 nylon suture was placed into the sclera 3 mm posterior to the corneoscleral limbus beneath and around the tube. This suture served to anchor the tube to the sclera and prevented its shift sideways postoperatively. A 5-0 Vicryl suture was ligated around the tube at its exit from the plate and closed tightly to occlude its lumen. This suture was self-absorbable and usually dissolved three days to three weeks postoperatively. The tube was trimmed bevel-up and then inserted into the anterior chamber through a track made with a 21-gauge needle 1.0 mm posterior to the corneoscleral limbus and parallel to the iris. The tube was secured by the previously placed nylon suture. The scleral graft was brought back to position and was sutured to the sclera covering the tube. The conjunctiva was closed with 7-0 Vicryl or silk sutures. Corticosteroids and antibiotics were injected subconjunctivally. In the early postoperative period, topical corticosteroids and cycloplegics were applied.

Results

Twenty-six males and 15 females were studied. The preoperative diagnoses included pseudophakic glaucoma in 16 eyes, aphakic glaucoma in six eyes, neovascular glaucoma in eight eyes, postkeratoplasty glaucoma in three eyes, posttraumatic glaucoma in three eyes, Sturge-Weber syndrome in one eye, congenital glaucoma in one eye, juvenile glaucoma in one eye, and Chandler syndrome in one eye. The previous surgical procedures in these 41 patients included cataract extraction with intraocular lens implantation in 16 eyes, cataract extraction without intraocular lens implantation in six eyes, one filtering operation in 18 eyes, more than one filtering operation in 20 eyes, penetrating keratoplasty in three eyes, and cyclocryotherapy in ten eyes. The mean age of the patients was 57 ± 8.2 years (range, 7 to 85 years). The mean preoperative intraocular pressure was 40 ± 13.2 mm Hg.

Thirty-two of the patients (78%) had postoperative intraocular pressure of 18 mm Hg or less. The mean postoperative intraocular pressure was 16 ± 6.6 mm Hg. The mean follow-up time was 16 months (range, four to 28 months). Visual acuity remained unchanged in 23 patients (56%), improved in nine patients (22%), and decreased in nine patients (22%). The causes of reduction in visual acuity included hypotony and cystoid macular edema (three patients), vitreous hemorrhage (two patients), retinal detachment (one patient), and apparent further progression of optic nerve damage in three patients.

There were no major intraoperative complications. Early hyphema appeared in four eyes (9.8%) that had neovascular glaucoma. It resolved within two days without any sequelae. Shallow anterior chamber and prolonged hypotony occurred in six patients (14.6%). A deep anterior chamber was present within two weeks after the operation in all patients. A peripheral choroidal effusion occurred in 15 eyes (36.6%).

Block of the tip of the tube in the anterior chamber occurred in six patients (14.6%). In three eyes the tip was blocked by fibrin, in two eyes by iris tissue, and in one eye by the vitreous gel. In each instance, Nd:YAG laser application to the tube's tip reopened the tube with subsequent increase of aqueous flow and immediate reduction of intraocular pressure.

Recession of the silicone tube to the anterior chamber angle occurred in two cases (4.9%). One eye required Nd:YAG laser application to the fibrin tissue that covered the tube's tip. Intraocular pressure remained controlled in both eyes.

Erosion of the tube occurred in one patient. This was one of two cases that required removal of the implant. Malignant glaucoma occurred in two patients (4.9%). Both eyes were pseudophakic with a history of angle-closure glaucoma. Nd:YAG laser hyaloidotomy was successful in both cases, with deepening of the anterior chamber and reduction of intraocular pressure.

Tenon's cyst formation occurred in three patients (7.3%), two to four months postoperatively. Two patients had glaucoma after penetrating keratoplasty, and one patient had juvenile glaucoma. In two patients, repeated needling of the cyst through the conjunctiva was sufficient to achieve control of intraocular pressure, whereas in one eye surgical excision of the Tenon's cyst was performed.

Vitreous hemorrhage occurred in two eyes (4.9%). In one patient it resolved after two months, whereas in the other patient vitreous opacification developed with reduction of visu-

al acuity from 20/100 to counting fingers at 20 cm, which required vitrectomy.

Retinal detachment occurred in one eye (2.4%). Initially suprachoroidal hemorrhage developed, subsequently accompanied by retinal detachment, with the retina adhering to the posterior intraocular lens surface. The patient required two choroidal tap procedures, removal of the implant, pars plana vitrectomy, and silicone oil injection to flatten the retina. Intraocular pressure remained high (60 mm Hg), and the patient required cyclocryotherapy, with subsequent intraocular pressure control at 12 mm Hg and visual acuity of counting fingers at 1 foot.

Discussion

The Molteno implant is a widely used aqueous drainage device for eyes with refractory glaucoma. Although our success of intraocular pressure control in these difficult cases is promising, complications occur with this procedure.

Modifications in operative technique, such as temporary ligation of the tube, the use of intracameral viscoelastic material, the use of needle track for insertion of the tube, and a donor scleral patch, have been reported to reduce some of the major postoperative complications substantially but have not totally eliminated their occurrence.[7,16-18] Despite the success of intraocular pressure control, however, postoperative sequelae and complications do occur.

Postoperative hyphema has been described in patients with neovascular glaucoma.[4] We detected hyphema in four eyes with neovascular glaucoma. This complication resolved within days and had no effect on the outcome of the operation.

Despite tight ligation of the tube, shallow anterior chamber and hypotony occurred in 14.6% of the eyes. This have been caused by aqueous leakage around the silicone tube despite the use of a 21-gauge needle track performed to introduce it into the anterior chamber. In all eyes, the anterior chamber regained its full depth within two weeks, but in three eyes visual acuity decreased because of persistent cystoid macular edema. We believe this complication is still one of the most serious after Molteno implant surgery, although its rate and severity were reduced with these modifications.

Other serious complications are suprachoroidal hemorrhage, vitreous hemorrhage, and retinal detachment. In one patient visual loss was caused by retinal detachment after suprachoroidal hemorrhage. A similar rate of retinal detachment after Molteno implant surgery has been reported by Minckler and associates,[10] and thus we believe the intraoperative modifications we used do not basically affect this rate. Vitreous hemorrhage occurred in two eyes (4.9%), with complete resolution of the bleeding in one eye and persistent fibrous organization that required vitrectomy in the other eye. The reasons for vitreous hemorrhage may be inadvertent scleral perforation or extension of suprachoroidal hemorrhage.

Less grave postoperative complications may be treated adequately upon diagnosis. Obstruction of the tip of the tube by fibrin, iris, and vitreous was detected in six eyes. All eyes were treated successfully by lasering the tube's tip and reopening the route for aqueous flow.[13] Trimming of the tube's tip bevel-up is an important intraoperative step that allows an easy approach to the blocked tube if necessary.

Recession of the tube in two eyes into the angle probably resulted from failure to attach the tube or the plate to the sclera. This complication must be monitored closely, because extrusion of the tube may occur during the early postoperative period. Obstruction of the tip of the tube by fibrin or iris may be corrected by laser surgery. One such patient responded favorably to laser treatment through a goniolens with subsequent reduction of intraocular pressure.

Malignant glaucoma was detected in two eyes (4.9%). Both eyes were pseudophakic, had had previous chronic angle-closure glaucoma, and responded well to Nd:YAG laser hyaloidotomy. The danger in such cases is from the shallow chamber and the developing pressure that push the tube against the corneal endothelium. In both eyes, prompt diagnosis and treatment resulted in rapid deepening of the anterior chamber with subsequent reduction of intraocular pressure without corneal damage.

Tenon's cyst with accompanying intraocular pressure increase occurred in three eyes (7.3%). All of these patients were relatively young (ages 21, 28, and 42 years) with inflamed eyes before surgery. The presumed excessive healing process of the young patient and the stimulatory effect of the inflamed eye to enhance the scarring may explain the active subconjunctival fibrosis in these eyes. Two eyes responded to repeated subconjunctival needling of the cyst, whereas in one eye only complete surgical re-

moval of the cyst resulted in good intraocular pressure control.

Focusing on postoperative complications of Molteno implant surgery should not lead to the impression that Molteno implant surgery is not effective. Knowing the possible complications may help in planning the operation, and in prevention and treatment of many of these complications. The intraoperative modifications reduce the rate and severity of complications, but further improvement is necessary. The use of intracameral viscoelastic material, donor scleral patch, a needle track for tube insertion, and temporary ligation of the tube help in reducing severe complications such as anterior chamber shallowing and hypotony, apposition of the tube to the corneal endothelium or the lens, and tube erosion.

However, other complications such as retinal detachment, vitreous hemorrhage, malignant glaucoma, obstruction of the tube, and Tenon's cyst formation are not affected by these modifications. Fortunately, most postoperative sequelae are transient or can be treated successfully either by laser treatment or additional surgery.

References

1. Sherwood, M. B., Joseph, N. H., and Hitchings, R. A.: Surgery for refractive glaucoma. Results and complications with a modified Schocket technique. Arch. Ophthalmol. 105:562, 1987.

2. Schocket, S. S., Nirankari, V. S., Lakhanpal, V., Richards, R. D., and Lerner, B. C.: Anterior chamber tube shunt to an encircling band in the treatment of refractory glaucomas. A long-term study. Ophthalmology 92:553, 1985.

3. Melamed, S., and Fiore, P.: Molteno implant surgery in refractory glaucoma. Surv. Ophthalmol. 34:441, 1990.

4. Ancker, E., and Molteno, A. C. B.: Molteno drainage implant for neovascular glaucoma. Trans. Ophthalmol. Soc. U.K. 102:122, 1982.

5. Brown, R. D., and Cairns, J. E.: Experience with Molteno long tube implant. Trans. Ophthalmol. Soc. U.K. 103:299, 1983.

6. Cairns, J. E.: The Molteno implant. Trans. Ophthalmol. Soc. U.K. 103:39, 1983.

7. Freedman, J.: Scleral patch grafts with Molteno setons. Ophthalmic Surg. 18:532, 1987.

8. Heuer, D. K., Abrams, D. A., Baerveldt, G., Galanis, J. C., Hasty, B., Minckler, D. S., and Martone, J. F.: Randomized clinical trial of single and double plate Molteno implants in patients with poor clinical prognosis. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1989, p. 282.

9. McDonnell, P. J., Robin, J. B., Schanzlin, D. J., Minckler, D., Baerveldt, G., Smith, R. E., and Heuer, D.: Molteno implant for control of glaucoma in eyes after penetrating keratoplasty. Ophthalmology 95:364, 1988.

10. Minckler, D. S., Heuer, D. K., Hasty, B., Baerveldt, G., Cutting, R. C., and Barlow, W. E.: Clinical experience with the single-plate Molteno implant in complicated glaucomas. Ophthalmology 95:1181, 1988.

11. Traverso, C. E., Tomey, F. K., and Al-Kaff, A.: The Molteno draining implant for the management of complicated glaucoma cases. Ophthalmology 94:80, 1987.

12. Molteno, A. C. B.: The use of draining implants in resistant cases of glaucoma. Trans. Ophthalmol. Soc. N.Z. 35:94, 1983.

13. Fiore, P. M., and Melamed, S.: Use of neodymium:YAG laser to open an occluded Molteno tube. Ophthalmic Surg. 20:201, 1989.

14. McClellan, K. A., and Billson, F. A.: Late development of localized band keratopathy in relation to a Molteno tube. Cornea 8:227, 1989.

15. Price, F. W., and Whitson, W. E.: Polypropylene ligatures as a means of controlling intraocular pressure with Molteno implants. Ophthalmic Surg. 20:781, 1989.

16. Egbert, P. R., and Lieberman, M. F.: Internal suture occlusion of the Molteno glaucoma implant for the prevention of post-operative hypotony. Ophthalmic Surg. 20:53, 1989.

17. Molteno, A. C. B., Van Biljon, G., and Ancker, E.: Two stage insertion of glaucoma drainage implants. Trans. Ophthalmol. Soc. N.Z. 31:17, 1979.

18. Molteno, A. C. B., Polkinghorne, P. J., and Bowbyes, J. A.: The Vicryl tie technique for inserting a draining implant in the treatment of secondary glaucoma. Aust. N.Z. J. Ophthalmol. 14:343, 1986.

A Comparison of Total and Partial Tenonectomy With Trabeculectomy

Kevin N. Miller, M.D., Marino Blasini, M.D., M. Bruce Shields, M.D., and Chih-Hsiang Ho, Ph.D.

We compared the results of two methods of tenonectomy at the time of trabeculectomy. Of 49 eyes, 23 were randomly assigned to a partial tenonectomy and 26 to a total tenonectomy. There was no statistically significant difference in the success rate between the two surgical groups using an upper limit of intraocular pressure of either 18 or 21 mm Hg as the criterion for success. There was no difference in the need for postoperative medications or further surgical intervention between the two groups. Although certain advantages exist with each technique, these findings suggest that equivalent results can be anticipated with either a total or partial tenonectomy.

THERE ARE DIFFERENT OPINIONS concerning the question of if and in what manner Tenon's capsule should be removed at the time of filtering surgery. The results of one study suggested similar control of glaucoma in patients undergoing trabeculectomy with or without tenonectomy.[1] We compared the results of two methods of tenonectomy at the time of trabeculectomy.

Patients and Methods

The patients in this study underwent trabeculectomy at the Duke University Eye Center performed by one of three of us (K.N.M., M.B., or M.B.S.). Patients with uncontrolled glaucoma despite maximum tolerable medical and laser therapy were included. Patients were excluded from the study if they had neovascular glaucoma, active anterior uveitis, previous cataract extraction, or previous failed filtering surgery. The patients were randomly assigned into one of two groups. One group underwent trabeculectomy with partial tenonectomy, and the other group underwent trabeculectomy with total tenonectomy. The surgical procedure was otherwise identical in both groups.

In both groups, a conjunctival incision was made in one of the superior quadrants, 8 to 10 mm behind the corneoscleral limbus. In the partial tenonectomy group, the incision was also carried through Tenon's capsule to the episclera. The two-layer incision was then extended laterally for two to three clock hours, and Tenon's capsule was dissected from underlying episclera forward to the corneoscleral limbus. The remainder of the trabeculectomy was performed in a standard fashion, which included a triangular-shaped, partial-thickness scleral flap, a 2 × 4-mm fistula, a peripheral iridectomy, and closure of the scleral flap with a single 10-0 nylon suture. Before closing the conjunctival incision, the free edge of Tenon's capsule was gently pulled away from the edge of the conjunctiva and the excess Tenon's capsule was excised, without interfering with the conjunctiva. The conjunctival incision was then closed with a running 10-0 polyglycolic acid suture on a fine, tapered, noncutting needle.

The total tenonectomy group underwent the same procedure except for the following variation. The conjunctival incision, 8 to 10 mm behind the corneoscleral limbus, was extended laterally for two to three clock hours but was not continued through Tenon's capsule. Instead, the dissection was carried forward to the corneoscleral limbus between the conjunctiva and the underlying Tenon's capsule. After this dissection was completed, Tenon's capsule was

Accepted for publication Nov. 28, 1990.

From the Department of Ophthalmology, Duke University Eye Center, Durham, North Carolina (Drs. Miller, Blasini, and Shields); and Department of Mathematical Sciences, University of Nevada, Las Vegas, Nevada (Dr. Ho).

Reprint requests to M. Bruce Shields, M.D., Department of Ophthalmology, Duke University Eye Center, Box 3802, Durham, NC 27710.

incised along the corneoscleral limbus slightly posterior to the hinge of the conjunctival flap, dissected posteriorly from underlying episclera, and excised near the level of the original conjunctival incision. The trabeculectomy was then completed in the usual fashion.

In both groups, atropine and an antibiotic-corticosteroid ointment were applied to the eye at the end of the procedure. These two medications were continued postoperatively two and four times daily for approximately one month.

A comparison was made of the characteristics of the partial and total tenonectomy groups. Preoperative data included mean age, race, gender, preoperative diagnosis, mean intraocular pressure, right vs left eye being operated on, and mean number of preoperative medications needed. Postoperative data included visual acuity, intraocular pressure, anterior chamber reaction, bleb characteristics, and fundus appearance. The anterior chamber depth was graded according to the following criteria: (1) deep, greater than or equal to one corneal thickness between midperipheral iris and overlying cornea; (2) shallow, from slit-shaped to one corneal thickness between the entire iris and overlying cornea; (3) extremely shallow, peripheral iris-corneal touch but no lens-corneal touch, no compression of the iris stroma, and no corneal decompensation; and (4) flat, lens-corneal touch, compression of the iris stroma, and corneal decompensation. The characteristics of the bleb were graded according to the following criteria: (1) localized (less than two clock hours), low to high height, avascular to partially vascular bleb, with few to many microcysts; (2) diffuse (greater than two clock hours), low to high height, avascular to partially vascular bleb, with none to many microcysts; (3) encapsulated, medium to high height, partially vascular to vascular bleb, with no microcysts; and (4) failing, low to flat height, partially vascular to vascular bleb, with no microcysts.

These observations were generally documented on postoperative Days 1, 2, and 7, and at two weeks, one month, and every two to four months thereafter for the duration of the study. For patients who returned for examination to their primary ophthalmologist, usually at the end of one month, some late postoperative data were obtained from these physicians.

A bleb was believed to be encapsulated if it had at least medium height, intraocular pressure of 25 mm Hg or higher in the period two to 12 weeks after filtering surgery, and no evidence of early bleb failure.

The patients were followed up for a minimum of five months or until an additional surgical procedure was needed. The intraocular pressure used in determining success or failure was either the last intraocular pressure measurement on follow-up examination or the intraocular pressure measured slightly before any additional surgical procedure. An eye was classified as having a failed procedure if the final intraocular pressure was less than 4 mm Hg or if additional filtering surgery with or without cataract extraction was needed. Two levels of qualified failure were also applied to the final results: final intraocular pressure greater than 21 mm Hg and 18 mm Hg. Final postoperative data also included the mean number of medications required and the mean follow-up time of each group.

Statistical analysis was used to compare the variables preoperatively and postoperatively in the two groups. The Mann-Whitney test was used in comparing the two groups with regard to patient age, preoperative intraocular pressure, number of preoperative medications, postoperative intraocular pressure, and mean follow-up time. The chi-square test was used for all other comparisons. Some of the subgroups with few patients were combined and the data were pooled when using the chi-square method to compare the preoperative diagnosis, the postoperative bleb appearance, and the number of medications required postoperatively.

Results

A total of 49 eyes of 44 patients were included in the study. Of these eyes, 23 were randomly assigned to a partial tenonectomy and 26 to a total tenonectomy.

In the partial tenonectomy group, the mean age was 64 years. Fifteen patients (17 eyes) were white and six patients (six eyes) were black. Sixteen patients were men (17 eyes) and five patients were women (six eyes). Eight right eyes and 15 left eyes were operated on. The diagnoses included the following: combined open- and closed-angle mechanism (one eye); primary open-angle glaucoma (18 eyes); pigmentary glaucoma (one eye); chronic closed-angle glaucoma (two eyes); and iridocorneal endothelial syndrome (one eye). The mean preoperative intraocular pressure was 27.8 mm Hg. The mean number of preoperative medications taken was 3.0.

In the total tenonectomy group, the mean age

was 61 years. Fifteen patients (16 eyes) were white and eight patients (ten eyes) were black. Eleven patients were men (12 eyes) and 12 patients were women (14 eyes). Seventeen right eyes and nine left eyes were operated on. The diagnoses included the following: combined open- and closed-angle mechanism (one eye); primary open-angle glaucoma (18 eyes); pigmentary glaucoma (one eye); chronic closed-angle glaucoma (one eye); angle-recession glaucoma (one eye); iridocorneal endothelial syndrome (one eye); inflammatory glaucoma (two eyes); and open-angle glaucoma after penetrating keratoplasty (one eye). The mean preoperative intraocular pressure was 30.5 mm Hg. The mean number of preoperative medications taken was 3.2.

There was no statistically significant difference between the characteristics in the two groups with two exceptions. There was a weak statistical significance between the two groups when comparing the sex of the patients ($P = .049$) and whether the right or left eye was operated on ($P = .033$).

Technically, preparation of the conjunctival flap required more sharp dissection with the total tenonectomy, although the degree of intraoperative bleeding was comparable for the two techniques. Two eyes in the partial tenonectomy group were complicated by inadvertent creation of a hole in the conjunctival flap.

Data from the early postoperative period (the first two months) are shown in the Table. There was no statistically significant difference between the two groups with regard to mean intraocular pressure, bleb characteristics, or anterior chamber depth.

Final intraocular pressure between 4 and 18 mm Hg was attained in 19 of 23 eyes (83%) in the partial group and 18 of 26 eyes (69%) in the total tenonectomy group, whereas intraocular pressure between 4 and 21 mm Hg was attained in 20 of 23 eyes (87%) in the partial group and 21 of 26 eyes (81%) in the total tenonectomy group. One patient in the total tenonectomy group had final intraocular pressure less than 4 mm Hg. There was no statistically significant difference in final intraocular pressure between the two groups ($P = .59$).

There was no statistically significant difference between the total and partial tenonectomy groups regarding the number of medications required by those patients with final intraocular pressure between 4 and 18 mm Hg ($P = .72$). One patient in the total tenonectomy group and two patients in the partial tenonectomy group developed encapsulated blebs. These patients were treated medically, and intraocular pressure decreased to an acceptable level.

One eye in the partial tenonectomy group and two in the total tenonectomy group required repeat filtering surgery, which was combined with cataract extraction in two of these patients. One patient in the partial tenonectomy group underwent drainage of serous suprachoroidal fluid and a subsequent combined cataract and filtering surgery procedure. In the total tenonectomy group, one patient required drainage of a suprachoroidal hemorrhage and subsequently underwent cataract extraction. The need for further surgical intervention was similar in the two groups. The mean follow-up period was 11.0 months for the partial tenonectomy group and 10.8 months for the total tenonectomy group.

TABLE
EARLY POSTOPERATIVE DATA

	MEAN INTRAOCULAR PRESSURE (MM HG)				BLEB APPEARANCE AT ONE MONTH (EYES)*				ANTERIOR CHAMBER DURING FIRST MONTH (EYES)†			
GROUP	DAY 1	DAY 2	WEEK 1	WEEK 6	LOCALIZED	DIFFUSE	ENCAPSULATED	FAILING	DEEP	SHALLOW	EXTREMELY SHALLOW	FLAT
Partial tenonectomy	6.1	5.5	4.9	12.1	1	15	0	3	1	4	15	3
Total tenonectomy	3.6	3.5	5.1	14.2	1	18	0	2	5	4	15	2
P value‡	.09	.21	.33	.42	—	—	—	—	—	—	—	—

*Data available on 19 eyes in the partial tenonectomy group and 21 eyes in the total tenonectomy group.

†Represents shallowest recorded depth during first postoperative month. Data available on 23 eyes in the partial tenonectomy group and 26 eyes in the total tenonectomy group.

‡Bleb appearance at one month, $P = .55$; anterior chamber during first month, $P = .44$.

Discussion

No consensus of opinion among glaucoma surgeons exists as to how Tenon's capsule should be managed at the time of filtering surgery. We have used both total and partial tenonectomy methods of managing Tenon's capsule during filtering surgery.

We did not find any statistically significant difference in the success rate between the two surgical groups using an upper limit of either 18 or 21 mm Hg as the criterion for success, nor did we find any difference in the need for postoperative medications or further surgical intervention between the two groups. These findings are consistent with those of Kapetansky,[1] who studied two groups of patients treated with a trabeculectomy. He used a subtotal tenonectomy in one group and left Tenon's capsule intact in the other. No difference between the two groups was noted with regard to postoperative intraocular pressure control.

The role of Tenon's capsule in the development of postoperative encapsulated blebs remains unclear. Only one patient in the total tenonectomy group and two in the partial tenonectomy group developed encapsulated blebs. Although these numbers are too small to make any significant comment with regard to the development of encapsulated blebs, these observations would seem to argue against the role of Tenon's capsule in this complication. Sherwood and associates[2] reported 79 encapsulated blebs among 607 eyes undergoing filtering surgery (13%), with only one of these having had a tenonectomy. Scott and Quigley[3] reported 18 encapsulated blebs in 181 eyes undergoing trabeculectomy and tenonectomy (10%).

Clearly, a total tenonectomy requires a more careful dissection and may be more likely to be associated with inadvertent hole formation than the subtenon's dissection and the partial tenonectomy technique. This would seem to favor a partial or no tenonectomy in most cases, despite the finding that the only cases of inadvertent hole formation of the conjunctival flap in our study were in the partial tenonectomy group. We have noted one intraoperative problem with the partial tenonectomy technique. When Tenon's capsule is unusually thick, the initial incision through conjunctiva and Tenon's capsule is more likely to be associated with brisk bleeding from vessels that are more difficult to see in the depths of a thick Tenon's capsule incision and, therefore, easier to damage and harder to cauterize. With the total tenonectomy technique, these vessels are more easily seen because the Tenon's capsule is dissected back from the corneoscleral limbus. For this reason, a total tenonectomy may be advantageous when this layer is unusually thick. Another possible advantage of a total tenonectomy, especially when the tissue is unusually thick, is to facilitate laser suture lysis, if this is anticipated in the early postoperative course.

In most cases, however, intraoperative advantages favor the partial tenonectomy. With this technique, the residual Tenon's capsule is not removed until just before closure of the conjunctival incision. This allows the surgeon or assistant to grasp the free edge of Tenon's capsule, thereby minimizing manipulation of the conjunctival flap with forceps, which may help reduce the chance of an inadvertent hole or conjunctival tear. An additional benefit of a partial or no tenonectomy is observed in patients who might require a double closure first of Tenon's capsule and then of the conjunctiva. This is becoming a more popular technique for patients who will receive postoperative 5-fluorouracil, in whom there is an increased risk of wound leak.[4]

In the final analysis, as with most aspects of glaucoma filtering surgery, the decision as to how to handle Tenon's capsule during the procedure rests with each surgeon's individual preference. Our findings suggest, however, that equivalent results can be anticipated with either a total or partial tenonectomy.

References

1. Kapetansky, F. M.: Trabeculectomy or trabeculectomy plus tenectomy. A comparative study. Glaucoma 2:451, 1980.

2. Sherwood, M. B., Spaeth, G. L, Simmons, S. T., Nichols, D. A., Walsh, A. M., Steinmann, W. C., and Wilson, R. P.: Cysts of Tenon's capsule following filtration surgery. Arch. Ophthalmol. 105:1517, 1987.

3. Scott, D. R., and Quigley, H. A.: Medical management of a high bleb phase after trabeculectomies. Ophthalmology 95:1169, 1988.

4. The Fluorouracil Filtering Surgery Study Group: Fluorouracil filtering surgery study one-year follow-up. Am. J. Ophthalmol. 108:625, 1989.

Therapeutic Ultrasound for the Treatment of Glaucoma

Ronald H. Silverman, Ph.D., Barbara Vogelsang, M.D., Mark J. Rondeau, and D. Jackson Coleman, M.D.

A multicenter clinical trial of therapeutic ultrasound for the treatment of glaucoma included 20 centers in the United States in which 1,117 treatments were performed on 880 eyes. The study was limited to patients with refractory glaucoma who had not benefited from conventional medical and surgical techniques. Approximately 782 of 1,117 treatments (70%) showed an initial decrease in intraocular pressure from a pretreatment mean of 38.1 mm Hg to 22 mm Hg or less. By Kaplan-Meier survival analysis, the single treatment success rate (intraocular pressure between 6 and 22 mm Hg) was 48.7% at six months posttreatment. When retreatment was used subsequent to failure, the one-year multitreatment success rate was 79.3%. The most common complications were an immediate posttreatment intraocular pressure increase lasting a few hours and mild iritis. Other complications included scleral thinning in 28 of 1,117 treatments (2.5%) and phthisis bulbi in 12 of 1,117 treatments (1.1%).

UNTIL RECENTLY the therapeutic options for patients with refractory glaucoma were severely limited. The most commonly performed procedure for patients who did not respond to surgical intervention was cyclocryotherapy. Although this procedure is effective in decreasing intraocular pressure, it is also associated with a high rate of ocular morbidity and patient discomfort. After observing that a focused beam of high-intensity ultrasound is capable of forming scleral lesions through thermal effects,[1,2] we began to investigate the possibility that this modality might be used for treatment of glaucoma either by decreased aqueous production through ciliodestruction or by increased outflow through the uvea or the transscleral route.

In 1985, we described the effects of high-intensity focused ultrasound on glaucoma in an animal model[3] and in a small group of patients with end-stage glaucoma.[4] Because of the encouraging results of these pilot studies, patients continued to be enrolled at the New York Hospital–Cornell Medical Center, and articles on a larger clinical study were published in 1986.[5,6]

In 1985, Cornell University Medical College, through the Cornell Research Foundation, licensed the ultrasound technology developed in our laboratory to Sonocare, Inc. Sonocare organized a multicenter clinical trial under Food and Drug Administration guidelines involving 20 centers, including Cornell University Medical College. One of us (D.J.C.) acted as the clinical monitor of this study. In 1988, after completion of the study enrollment goals and analysis of results, the procedure was approved by the Food and Drug Administration as safe and efficacious.

Reports have been published regarding the results of certain centers involved in this study.[7,8] We provide a comprehensive summary of the results obtained on 1,117 treatments of 880 eyes treated at 20 centers during the course of the study and examine the effect of treatment variables, glaucoma type, lens status, and demographics in terms of success rates. Additionally, we provide comprehensive documentation of patient discomfort, complications, side effects, and changes in visual acuity and medication levels after treatment.

Accepted for publication Dec. 12, 1990.

From the Department of Ophthalmology, Cornell University Medical College, New York, New York. This study was supported in part by Research to Prevent Blindness, Inc., the Dyson Foundation, and the Rudin Foundation. The multicenter clinical trial was sponsored by Sonocare, Inc. The device described in this article is licensed to Sonocare, Inc., by the Cornell Research Foundation, Ithaca, New York. Dr. Coleman has a proprietary interest in this technique. Licensing fees help support the Department of Ophthalmology, Cornell University Medical Center.

Reprint requests to D. Jackson Coleman, M.D., Department of Ophthalmology, Cornell University Medical College, 1300 York Ave., New York, NY 10021.

Patients and Methods

Description of the technique—Transducers having an 80-mm outer diameter, 90-mm focal length, and frequency of 4.6 MHz were used in all centers involved in this study. The transducers produced an ultrasound beam with a focal zone having a diameter of 0.4 mm and a length of 3.0 mm. The transducer assembly included a diagnostic A scan (for ranging) and a coaxial fiberoptic aiming light contained in a water-filled plastic cone. A description of the therapeutic ultrasound device and the biophysical details of lesion formation has been previously reported.[9]

After giving informed consent, the patients were given retrobulbar anesthesia and treated on an outpatient basis. In some instances, children were treated under light halothane anesthesia.

The transducer was coupled to the eye with a sterile, saline-filled water bath, similar to that used in immersion ultrasonography. This was necessary because ultrasound will not propagate through air. Using the aiming light and the cofocal A scan, the transducer focal zone was directed onto the sclera at a distance of 2 to 3 mm from the corneoscleral limbus. Under the study protocol, four to six five-second applications were to be made with a radiation force of 3 g. The positioning of the applications in clock hours was recorded, though not specified, because this was not found to be an important factor in earlier studies and retreatment over the same zone at a later date was not precluded.

Study organization—Each of the 880 patients enrolled in this study was treated at one of 20 centers located in the continental United States. In addition to the principal investigator, most centers had additional physicians approved to perform the procedure. Patient follow-up and recording of data were performed by the treatment centers or by the referring ophthalmologists.

The clinical trial was limited to patients with refractory glaucoma who had not responded to conventional maximal medical or surgical therapy. Surgical procedures included argon laser trabeculoplasty, filtering procedures, Molteno tubes, and cryopexy. A small number of patients not fulfilling the refractory glaucoma requirement were treated under individual waivers from the Food and Drug Administration.

Before treatment, demographic and clinical data were recorded for each patient, including pretreatment visual acuity, intraocular pressure, type and cause of glaucoma, surgical and medical treatment history, and cornea, lens, angle, vitreous, and retinal status. At the time of treatment, treatment variables (number of applications, focal zone depth, radiation force, and lesion location) were recorded, as were type of anesthesia, medications, and complications, if any. Standardized report forms for the study, which included intraocular pressure, visual acuity, visual fields, medication, discomfort, complications, and status of various ocular structures, were completed at two to five hours, one day, one week, and one, three, six, and 12 months after treatment. Copies of all reports were forwarded by the manufacturer to the clinical monitoring center for analysis.

Statistical evaluation—Treatment efficacy was assessed by the examination of changes in the average intraocular pressure over time and the use of Kaplan-Meier lifetable (survival) analysis, in which failure was defined as either hypotony (intraocular pressure less than or equal to 5 mm Hg) or uncontrolled intraocular pressure. Uncontrolled intraocular pressure was alternately defined as intraocular pressure exceeding a threshold of either 22 or 25 mm Hg. Eyes subsequently treated with ultrasound or any other form of glaucoma therapy (other than drug therapy) were also classified as failures.

Changes in visual acuity were expressed in terms of Snellen lines. Counting fingers, hand motions, light perception, and no light perception were each counted as one line.

Results

Study population—Of 880 patients, 446 were male and 427 were female. (The sex of seven patients was not recorded.) Six hundred seventy-one patients were white, 152 were black, and 11 were classified as other. (The race of 46 patients was not recorded.) The eyes of 298 patients were phakic and 514 were aphakic. (The lens status of 68 patients was not recorded.) The types of glaucoma included the following: congenital (71 patients); primary open-angle (205 patients); primary closed-angle (37 patients); secondary open-angle (88 patients); secondary closed-angle (414 patients); and unclassified (65 patients). The types of secondary glaucoma included the following: neovascular

(158 patients); uveitic (69 patients); aphakic or pseudophakic (105 patients); traumatic (40 patients); and other types or unclassified (130 patients). Patient age ranged from 2 to 99 years (mean, 54.2 years). The mean intraocular pressure before treatment was 38.1 mm Hg. The average pretreatment visual acuity was between 20/200 and 20/400.

Of the 1,117 ultrasound treatments, 880 (78.8%) were initial treatments, 205 (18.4%) were first retreatments, and 28 (2.5%) were second retreatments. Three eyes were treated four times and one eye was treated five times.

Treatment efficacy—The mean intraocular pressures before and after treatment are shown in Figure 1. During the course of the study, we found that some patients had posttreatment intraocular pressure increase. For this reason, several centers selectively reported intraocular pressure starting immediately after treatment. These reports showed an average increase in intraocular pressure of 22.8 mm Hg immediately after treatment.

By two to five hours after treatment, the mean intraocular pressure was virtually the same as the pretreatment level. At this time, intraocular pressure increase of 5 mm Hg or more was recorded in only 83 of 459 reports (18%). By one day posttreatment, only 65 of 808 reports (8%) showed increased intraocular pressure, and by one week posttreatment, 25 of 844 reports (3%) showed intraocular pressure increases above pretreatment levels.

By one day after treatment, 323 of 808 reports (40%) showed an intraocular pressure decrease of 10 mm Hg or more. At one week and one month, the number of eyes with intraocular pressure reduction of 10 mm Hg or more was 582 of 844 (69%) and 530 of 869 (61%), respectively. At one month or more after treatment, 228 of 994 reports (23%) showed intraocular pressure decrease of 25 mm Hg or more (median decrease, 14 mm Hg).

Treatment success rates, evaluated by survival analysis with intraocular pressure failure thresholds of 22 and 25 mm Hg, are shown in Figure 2 (top). Eyes with intraocular pressure above these thresholds or 5 mm Hg or less were classified as failures. Statistically, failures taking place at any point during the study lowered the cumulative success rates for all subsequent intervals, whereas nonfailures were counted only for the duration of follow-up.

The results for a single treatment show 279 to 335 of 1,117 treatments (25% to 30%) did not respond to treatment or failed in the first month after treatment. At six months, cumulative success rates of 54.5% and 48.7% were observed, using the 25- and 22-mm Hg thresholds. At one year, the success rates were 41.9% and 38.1%, respectively.

These results indicate that of the approximately 70% to 75% of eyes that did show an initial response to treatment, 60% were still successfully controlled without retreatment after one year. Since eyes that failed to respond to treatment or that failed after some time can be retreated, the success rates obtained using single treatment survival analysis underestimate the technique's potential for control of intraocular pressure.

The success rates for multiple treatments, in which the duration of intraocular pressure control by one or more treatments is determined,

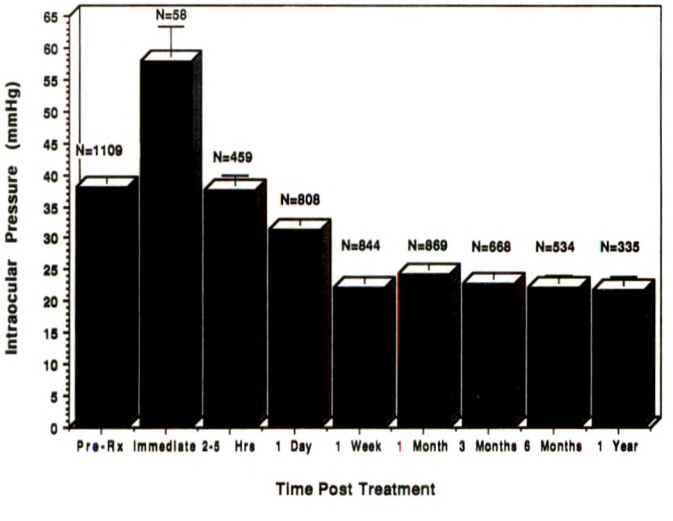


Fig. 1 (Silverman and associates). Mean intraocular pressures ±2 standard error before and at specified intervals after treatment. Number of reports received at each interval, N, are indicated above each bar.

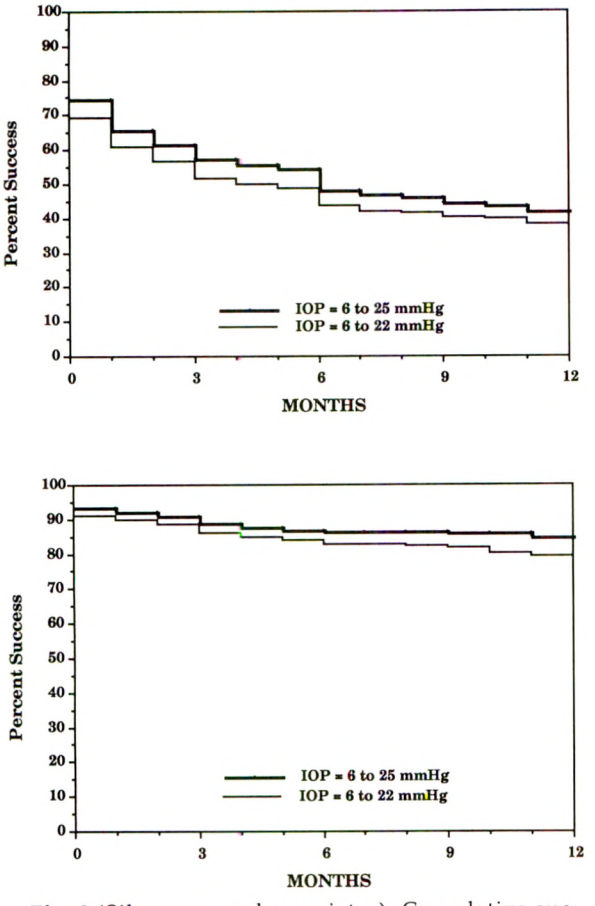


Fig. 2 (Silverman and associates). Cumulative success rates computed with Kaplan-Meier survival analysis. Top, Survival curves for single treatment. Bottom, Survival curves in which retreated eyes are not classified as failures. (Failures not retreated at least once are excluded.)

are shown in Figure 2 (bottom). Since this analysis was designed to determine the efficacy of the multitreatment regimen, eyes that failed after the initial treatment without at least one attempt at retreatment were not considered. Of the 559 that satisfied this criteria, six-month success rates of 87.0% and 83.9% were found, using intraocular pressures of 25 and 22 mm Hg as the upper cutoffs. The corresponding one-year success rates were 84.8% and 79.3%.

Comparative analyses—To study the effect of treatment and clinical variables, such as glaucoma type, previous treatment history, and pretreatment ocular status, we examined the success percentage at six months posttreatment. A statistical (log rank) test for the probability that the difference in the cumulative success rates among the tested groups might have occurred by chance is given in Table 1. In this analysis, success was defined as maintenance of intraocular pressure between 6 and 25 mm Hg after a single treatment.

Effect of number of applications—Eyes were divided into two groups: those given seven or more applications and those given six or fewer applications. Eyes given more than six applications had a significantly higher success rate. This is consistent with previously reported results, which also indicated that seven or more treatments had a greater intraocular pressure lowering effect but a higher complication rate.

Effect of patient age—Patients were divided into four age groupings: 15 years or younger, 16 to 35 years, 36 to 65 years, and older than 65 years. The results showed that the success rate is lowest in children and highest in patients older than 65 years. There appears to be an almost direct relationship between age and success rate. This is somewhat different than earlier findings in which it appeared that children had the lowest success rate, but no significant differences were found among the success rates in adults as a function of age.[5]

Response referred to pretreatment visual potential—Although the study was limited to eyes with refractory glaucoma, it was of interest to determine the efficacy of therapeutic ultrasound in eyes that retained a high degree of visual function. For this purpose, we stratified the population into two groups: those with visual acuity of 20/100 or better and those with visual acuity worse than 20/100. The results indicated that the success rate among eyes with good visual function was significantly higher than in those with poor visual potential.

Response referred to glaucoma type—Analyses stratified according to type of glaucoma and cause (for secondary glaucomas) indicated that therapeutic ultrasound was most effective in patients with primary open-angle glaucoma, somewhat less successful for secondary glaucomas, and least successful with congenital glaucoma. The low success rate in congenital glaucoma may be caused by correlation with patient age.

Among the eyes with secondary glaucoma, the highest success rate was found for glaucoma secondary to uveitis, closely followed by aphakic, pseudophakic, and traumatic glaucoma. Eyes with neovascular glaucoma had the lowest success rate.

Other factors—Evaluation of race, sex, and lens status showed no significant correlation with treatment outcome. Retreated eyes were found to have a somewhat higher success rate

TABLE 1
COMPARATIVE SINGLE-TREATMENT SUCCESS RATES

VARIABLE	GROUP	NO.	SIX-MONTH SUCCESS* PERCENTAGE	P VALUE
No. of applications	≤ 6	767	50.3	.0001
	> 6	307	65.3	
Treatment	Initial	854	53.7	.4930
	Retreatments	226	57.6	
Age (years)	≤ 15	71	44.1	.0078
	16–35	173	50.2	
	36–65	442	53.6	
	> 65	390	59.4	
Sex	Male	558	54.3	.6140
	Female	515	54.2	
Race	White	828	53.1	.5735
	Black	186	58.2	
	Other	18	46.9	
Pretreatment visual acuity	≥ 20/100	282	66.3	<.0001
	< 20/100	700	49.4	
Lens status	Phakic	364	52.6	.2141
	Aphakic	643	53.7	
Glaucoma type	Congenital	100	50.0	.0003
	Primary open angle	191	62.3	
	Primary closed angle	36	71.4	
	Secondary open angle	122	50.2	
	Secondary closed angle	500	52.5	
Secondary glaucomas	Neovascular	191	40.4	.0001
	Uveitic	85	67.8	
	Aphakic	132	51.3	
	Traumatic	54	51.4	

*Success was classified as intraocular pressure of 6 to 25 mm Hg.

than eyes after the initial treatment, but this difference was not found to be statistically significant.

Variation among study centers—Comparative results for the 20 centers are shown in Table 2. All centers except Cornell are numerically coded. Single-treatment, six-month success rates, and the mean number of complications per eye were recorded for each center.

Cornell, which included eyes treated with higher intensities of ultrasound and with greater numbers of applications, had the largest number of cases and the second highest success rate among the study centers. Of the four centers with 100 or more cases, three had better than average success rates, and the fourth was close to the mean. This observation suggests that operator experience is a factor in successful treatment outcome.

Most of the difference between the Cornell results and those of the rest of the study can be largely attributed to the difference between the initial success rates of 90% for Cornell compared with 70% for the rest of the study. For both groups, the success percentage subsequently decreased by 30% to 35% over the course of the year.

Cornell's higher success rate was accompanied by a much higher incidence of phthisis bulbi and prephthisis bulbi. Of the 12 eyes with phthisis bulbi, ten occurred at Cornell. The high incidence of this complication at Cornell was related to the relatively greater number of applications given to many of these patients. More applications produced a greater intraocular pressure lowering effect but increased the risk of hypotony. Cornell also had a higher incidence of scleral thinning and corneal changes (bullous keratopathy). Center 1 reported corneoscleral lesions in 37 of 43 cases, which accounted for almost 35% of such occurrences in the entire study. This center placed lesions closer to the cornea than the 2 to 3 mm recommended by the study protocol.

Visual acuity—Changes in visual acuity in Snellen lines were evaluated at one, three, six, and 12 months after treatment. The results showed that approximately 173 of 863 patients (20%) demonstrated a decrease in visual acuity of two or more lines at each interval; visual acuity in 615 patients (71%) stayed the same; and 75 patients (9%) showed an improvement of two or more Snellen lines.

The causal factors relating to visual acuity changes were evaluated by analysis of variance. In this analysis, we considered the intraocular pressure at each interval and the type and cause of the glaucoma. The analysis was made using pretreatment visual acuity as a control variable. This was necessary since a patient with good visual acuity was far more likely to have demonstrable sight loss than patients with poor visual acuity.

TABLE 2
VARIATION OF SINGLE-TREATMENT SUCCESS RATES AMONG TREATMENT CENTERS

CENTER	NO.	SIX-MONTH SUCCESS* PERCENTAGE	COMPLICATION RATE
Cornell	242	74.2	0.425
1	43	44.7	2.047
2	39	42.5	0.231
3	117	67.5	0.111
4	53	45.9	0.113
5	16	53.4	1.562
6	29	16.9	0.931
7	25	45.2	0.120
8	101	58.4	0.287
9	120	53.5	0.708
10	4	50.0	0.500
11	15	38.9	0.400
12	22	81.3	0.182
13	17	32.4	1.118
14	66	46.3	1.167
15	62	26.7	0.984
16	21	48.5	0.381
17	8	12.5	1.000
18	8	37.5	1.500
19	71	33.5	0.253

*Success was classified as intraocular pressure of 6 to 25 mm Hg.

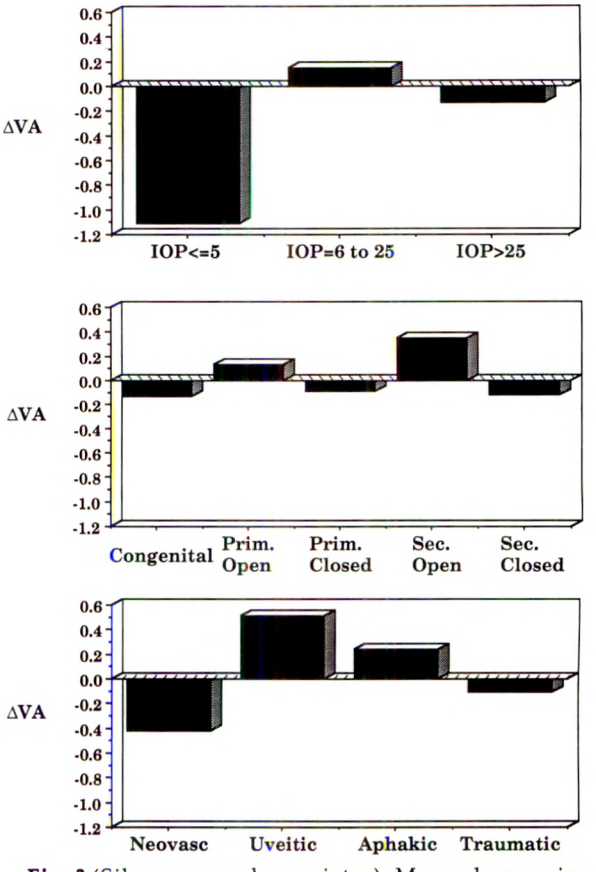


Fig. 3 (Silverman and associates). Mean changes in visual acuity (ΔVA) in Snellen lines, controlling for pretreatment visual acuity. Top, Effect of intraocular pressure (IOP) after treatment. Middle, Visual acuity changes in relation to glaucoma type. Bottom, Visual acuity changes in relation to secondary glaucoma classifications.

The mean results, summarized in Figure 3, show that decreases in visual acuity occurred in eyes that were hypotonous or had uncontrolled intraocular pressure. Eyes with congenital and secondary closed-angle glaucoma appeared to be the glaucoma types that most consistently lost visual acuity. These features support the hypothesis that decreased visual acuity is related to treatment failure rather than the treatment itself. Among the secondary glaucomas, eyes with neovascular glaucoma tended to show decreased visual acuity, which, because of the higher failure rate and possible progression of the underlying disease state, is also consistent with this hypothesis.

Patient discomfort—Patient discomfort was classified into one of four groups: none, mild, moderate, or severe. The results are plotted in Figure 4. At two to five hours immediately after treatment approximately 155 of 445 reports (35%) indicated mild discomfort, and 40 reports (9%) indicated moderate to severe discomfort. At the end of the first week, only 124 of 685 reports (18%) indicated mild discomfort and 24 reports (3.5%) indicated moderate or severe discomfort.

Complications—Complications were categorized as either technical or method-related. Corneoscleral lesions and eyelid burns were considered technical complications since they are caused by misdirection of the beam or patient movement.

The technical complications included corneoscleral lesions in 106 eyes and eyelid burn in 16 eyes. The method-related complications included the following: mild iritis (210 eyes); moderate iritis (70 eyes); severe iritis (four eyes); mild uveitis (28 eyes); moderate uveitis (14 eyes); severe uveitis (one eye); phthisis bulbi (12 eyes); ruptured conjunctivitis (seven eyes); hemorrhaged conjunctiva (12 eyes); conjunctivitis (two eyes); corneal edema and keratopathy (30 eyes); keratitis (four eyes); scleral thinning (16 eyes); staphyloma (eight eyes); scleral perforation (four eyes); flat anterior chamber (four eyes); hyphema (three eyes);

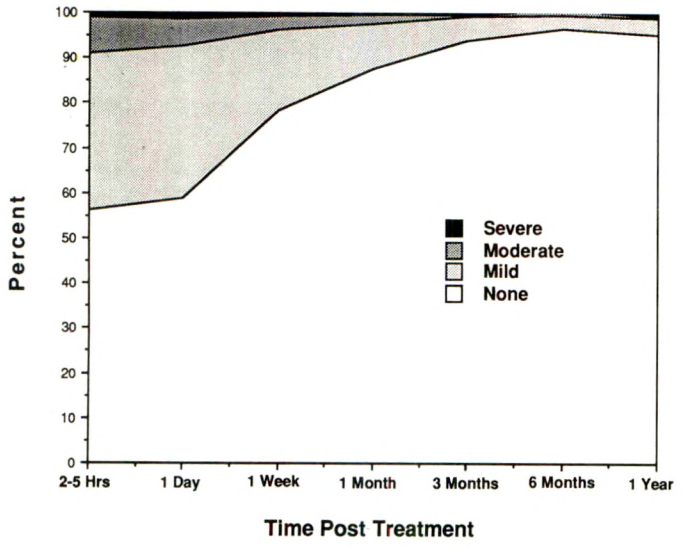


Fig. 4 (Silverman and associates). Patient discomfort (none, mild, moderate, or severe) expressed as percentile of reports at specified intervals after treatment.

pupillary block (three eyes); ciliary body hemorrhage (two eyes); iris rubeosis (four eyes); cataract (15 eyes); vitreous hemorrhage (one eye); vitreitis (one eye); cystoid macular edema (two eyes); macular membrane (one eye); retinal detachment (one eye); and choroidal effusion or detachment (eight eyes).

Complications were counted on the basis of occurrence rather than incidence. For example, in a case where corneal edema was reported at one week and at one month posttreatment, the complication was counted as having occurred once. In cases of iritis and uveitis, where the complication was graded from mild to severe, the most severe occurrence was counted. Any number of different complications may have been counted by occurrence for each case.

Corneoscleral lesions occurred in more than 9% of treatments. This complication results from placement of the focal zone too close to the corneoscleral limbus. Of the 106 occurrences of this complication, 37 took place at a single participating center (Center 1). Excluding the results of this treatment center would give an occurrence rate of 6.4%.

The most common medical complication was iritis. This was generally mild and similar to that noted after laser or cyclocryotherapy. As such, it was generally easily controlled with topical corticosteroids. By three months posttreatment, the incidence of iritis decreased to 3.7% from 24% at one day posttreatment.

Sixteen cases of scleral thinning, eight staphylomas, and four scleral perforations occurred during the course of the study for an aggregate occurrence of 2.5%. Half of the cases of scleral thinning or staphyloma occurred at Cornell, although no cases of perforation occurred at this center. Posttreatment bullous keratopathy and corneal edema were usually transient and corresponded, in part, to increased intraocular pressure posttreatment.

In 12 eyes, a previous cataract worsened; in three others, a cataract developed subsequent to treatment. Cataract progression was most often correlated with occurrence of hypotony. The incidence of hypotony, defined as intraocular pressure less than or equal to 5 mm Hg, ranged from 2.2% to 5.4% between one month and one year after treatment. Most cases were transient, with phthisis bulbi occurring in 1.2% of treatments.

Changes in medication—The study protocol specified that patients were to continue taking glaucoma medication at their physician's discretion subsequent to treatment. Medications were divided into four groups: beta-blockers, carbonic anhydrase inhibitors, epinephrine preparations, and miotics. For each medication group, a point system was used to rate the effective daily dosage based on the strength of the medication and the frequency of use.

Among successfully treated cases, medication level, as a whole, was reduced by 19.9% and 28.6% at three and 12 months, respectively. In contrast, among failures, medication was decreased by only 3.4% and 6.4% at three and 12 months, respectively. Beta-blockers showed a decrease of about 10% after one month. The level of carbonic anhydrase inhibitors decreased with time, with a 50% reduction at one year. A similar pattern was observed for epinephrine preparations, which registered a 45% reduction at one year. Miotics showed a 20%

decrease over pretreatment levels over the entire year.

Discussion

High-intensity focused ultrasound is the only nonmedicinal glaucoma treatment to be evaluated in a prospective multicenter clinical trial under the Food and Drug Administration investigational device and premarket approval process. Although the ultimate place of focused ultrasound in the armamentarium of glaucoma procedures awaits further clinical experience, this study demonstrates the safety and efficacy of the procedure, and more generally the usefulness of focal lesion-producing techniques as a means of treating glaucoma.

Three factors are of paramount importance in the diagnosis and management of glaucoma: increased intraocular pressure, visual field abnormalities, and pathologic optic nerve cupping. Visual field changes and optic nerve cupping were not used as efficacy criteria in this study because most of the enrolled patients had advanced glaucoma with poor visual acuity and advanced disk cupping. Monitoring of intraocular pressure was considered the most objective measure of efficacy.

We have previously reported a 60% one-year success rate for 137 single treatments at Cornell with successful intraocular pressure control defined as being in the 6- to 25-mm Hg range.[5] Using the same standard in this report, we show a 58.5% success rate on 242 cases.

For the study as a whole, the single-treatment, one-year success rate of 42% was significantly lower than Cornell's success rate. This can be attributed to two factors: the Cornell center tended to treat patients with more applications (which resulted in both a greater intraocular pressure lowering effect and a consequent higher incidence of hypotony and scleral thinning), and operator experience. The first factor is supported by the observation that the primary difference between the success rates of Cornell and the rest of the study occurred immediately after treatment. After one month, the rate of decrease of the success percentage in the survival curves was virtually the same for both groups. The second factor is supported by the observation that the centers with the most cases tended to have the highest success rates. The three study centers with the most experience, such as Cornell, have mean success durations for a single treatment of over one year.

A realistic assessment of therapeutic ultrasound as a treatment modality must include retreatment. It is apparent that the risk:benefit ratio is optimized by using six to seven applications per session and retreating when necessary, using ultrasound in fractional applications, as in certain types of laser therapy such as argon laser trabeculoplasty or panretinal photocoagulation. With retreatment, we find an 84% success rate with 6 to 22 mm Hg as the success criterion. Retreatment of failed cases is a viable course because of the following: the procedure is performed on an outpatient basis; it has high patient acceptance because of the minimal patient discomfort; retreatments have success rates comparable to initial treatments; the complication rate is low; and treatment does not preclude later ultrasonic or surgical treatment near the application sites.

The most common technical complication was formation of corneoscleral lesions. These occurred as a consequence of patient movement because of incomplete anesthesia or placement of the beam too close to the corneoscleral limbus. The frequency of technical complications tends to decrease with operator experience.

Although ultrasound is capable of causing an immediate cataract if intentionally aimed at the lens, this complication was not reported during the course of the study. As has also been noted, ultrasound can damage intraocular lenses or their haptics[10] if applied directly. Although numerous pseudophakic eyes were treated during the course of this study, there were no reports of intraocular lens damage.

Phthisis bulbi and scleral thinning were correlated with the number of applications. Since the number of applications also correlates with success rate, the decision on how vigorously to treat a given patient involves analysis of a risk:benefit ratio. The treatment protocol for this study specified six applications per treatment. This decision, based on earlier experience at Cornell and at Center 1, resulted in far lower incidences of phthisis bulbi and scleral thinning, as compared to Cornell, but at the same time resulted in a lower success rate. The higher incidence of scleral thinning in children than in adults seems to be related to a difference in juvenile compared with adult collagen. Thus, children, who also have a lower success rate, are generally less suitable candidates for this therapy.

The study protocol required the recording of data at two to five hours after treatment, but at the time the protocol was designed, the dynam-

ics of intraocular pressure change immediately after treatment were not well understood. At two to five hours after treatment, only 18% of patients enrolled in the multicenter study showed an intraocular pressure increase of more than 5 mm Hg. We now know that by two hours after treatment, intraocular pressure is already on the descending part of the posttreatment pressure curve. Although the protocol did not require pressure observations before two to five hours posttreatment, several centers recorded intraocular pressure starting immediately after treatment. These reports indicate that substantial intraocular pressure increases, usually lasting less than an hour, may occur immediately after therapy. We therefore now recommend that patients, especially those with marginal visual function, be carefully monitored immediately after treatment. Those cases showing a substantial intraocular pressure increase can be treated with an acetazolamide injection, a mannitol infusion, or paracentesis. Many clinicians advocate paracentesis in all aphakic or pseudophakic eyes. Posttreatment intraocular pressure increase is not a unique sequela of ultrasound but may follow any high-energy (laser or ultrasound) or heat (diathermy) therapy, because of contraction or shrinkage of the sclera.

Several mechanisms have been suggested as the mode of action for therapeutic ultrasound in glaucoma therapy.[11] These include the following: decreased inflow by either direct ciliodestruction or indirect ciliodestruction through damage to the vascular supply of the ciliary body; increased outflow through the trabecular meshwork caused by pulling of the contracted sclera upon the ciliary body; direct outflow through the atrophic pars plana and thinned sclera; uveoscleral outflow from the anterior chamber through loosened stromal connective tissue of the ciliary body and thinned sclera (minidialysis clefts) (Françoise Valtot, oral communication, 1990); and an ocular irritative response.[12] Evidence for these mechanisms depends largely on histologic evaluation and aqueous fluorophotometry and, to some extent, remains controversial. Although all of these mechanisms might make some contribution to the intraocular pressure lowering effect, ciliodestruction and formation of minidialysis clefts seem the simplest explanations for prolonged intraocular pressure reduction. On this assumption current studies are now investigating the effect of setting the focal point 1 mm deeper than the scleral surface. This may have the dual effects of both producing increased ciliodestruction and cleft formation while reducing the incidence of undesirable scleral changes.

Ultrasound has also been used for restoration of failed trabeculectomy filtering blebs.[13] In this procedure, one to three applications are made on and adjacent to the sealed bleb. Local heating appears to break the collagen fibers that have closed the bleb. In this case, because the mechanism of this procedure is based upon scleral changes, we continue to place the focal point on the scleral surface. Restorations of failed blebs were excluded from the current study.

Glaucoma procedures that act primarily by ciliodestruction include cyclocryotherapy, transscleral cyclophotocoagulation, transpupillary cyclophotocoagulation, and intraocular cyclophotocoagulation using the endoscopic or transpupillary visualization technique. The two techniques that bear the closest resemblance to therapeutic ultrasound are cyclocryotherapy and transscleral Nd:YAG cyclophotocoagulation.

Although cyclocryotherapy is effective in lowering intraocular pressure in eyes with refractory glaucoma, it is usually accompanied by a relatively high incidence of phthisis bulbi, progression of visual acuity loss to no light perception, and extreme discomfort. Cyclocryotherapy, therefore, has been and remains a procedure of last resort. Use of transscleral Nd:YAG cyclophotocoagulation, like ultrasound, involves treatment at 2 to 3 mm from the corneoscleral limbus while the eye is under retrobulbar block. Because the focal point of the laser is narrower than the focus of the ultrasound beam (approximately 0.07 mm vs 0.4 mm), greater numbers of applications must be made during treatment. Typically, between 30 and 40 applications are made over 360 degrees (as compared to approximately six applications for ultrasound). Retreatment may be performed if control of intraocular pressure is not maintained.

Several small studies (30 patients or less) describing the use of transscleral Nd:YAG laser have been reported.[14-16] These studies indicated multitreatment success rates of 55% to 86%, using varying intraocular pressure thresholds, with mean follow-up of three to nine months. A study involving 100 patients reported a 51% single-treatment success rate and a 65% multiple-treatment success rate at six months after treatment, in which success was defined as intraocular pressure of 7 to 20 mm Hg.[17] These results are comparable to the six-month, single, and multiple-treatment success rates of 49%

and 84% at 6 to 22 mm Hg reported in this study. The incidence of serious complications reported in these studies[14-17] appears higher than reported for therapeutic ultrasound. The study by Hampton and associates,[17] the largest of the studies, reported decreased visual acuity (more than two Snellen lines) in 47% of successfully treated cases. Other complications included posttreatment intraocular pressure increase, hypotony, and inflammation.

Many techniques are now available for the treatment of refractory glaucoma. To date, more than 2,000 eyes have been treated in the United States and Europe[18,19] with high-intensity focused ultrasound. This technique proved to be at least as effective and considerably less traumatic than cyclocryotherapy, and it seems to be comparable, if not preferable, to transscleral photocoagulation, in terms of success rate and complications. Additionally, the technique is useful in restoring failed filtering blebs.

High-intensity focused ultrasound is one of the most extensively tested and documented forms of therapy for the treatment of glaucoma other than drug therapy. The design and population size of our study have allowed the documentation of prognostic indicators and determination of the safety and efficacy of a well-defined treatment protocol. These data provide a benchmark for the evaluation of ultrasound protocols applied to a broader, nonrefractory glaucoma population, and for all forms of externally applied focal lesion procedures for the treatment of glaucoma.

Acknowledgment

The principal investigators for the multicenter trial were the following: Hugh Beckman, M.D., Sinai Hospital of Detroit, Southfield, Michigan; Walter F. Bundy III, M.D., St. Mary's Hospital, Richmond, Virginia; James G. Ferguson, M.D., University of South Carolina School of Medicine, Columbia, South Carolina; Murray A. Johnstone, M.D., Swedish Hospital Medical Center, Seattle, Washington; Richard A. Kieler, M.D., Lexington Clinic, Lexington, Kentucky; Kathleen Lamping, M.D., Mt. Sinai Medical Center, Cleveland, Ohio; Ralph Levene, M.D., Brookwood Hospital Medical Center, Birmingham, Alabama; Alan I. Mandell, M.D., St. Francis Hospital, Memphis, Tennessee; John Mensher, M.D., Mason Clinic, Seattle, Washington; Ivan R. Schwab, M.D., West Virginia University Medical Center, Morganville, West Virginia; Steven S. Searl, M.D., University of Rochester School of Medicine, Rochester, New York; Neal Sher, M.D., Mt. Sinai Hospital, Minneapolis, Minnesota; Robert L. Shields, M.D., Porter Memorial Hospital, Denver, Colorado; Richard J. Simmons, M.D., New England Glaucoma Research Foundation, Boston, Massachusetts; Jess Smith, M.D., Methodist Hospital, Houston, Texas; George W. Tate, M.D., Carolina Eye Associates, Southern Pines, North Carolina; Stuart A. Terry, M.D., Baptist Medical Center Hospital, San Antonio, Texas; Daniel G. Vaughan, M.D., O'Connor Hospital, San Jose, California; and Richard Wilson, M.D., Wills Eye Hospital, Baltimore, Maryland.

References

1. Coleman, D. J., Lizzi, F. L., and Jakobiec, F. A.: Therapeutic ultrasound in the production of ocular lesions. Am. J. Ophthalmol. 86:185, 1978.

2. Coleman D. J., Lizzi F. L., Chang S., and Driller J.: Applications of therapeutic ultrasound in ophthalmology. In Kurjak, A. (ed.): Progress in Medical Ultrasound. Amsterdam, Excerpta Medica, 1981, pp. 263–270.

3. Coleman, D. J., Lizzi, F. L., Driller, J., Rosado, A., Chang, S., Iwamoto, T., and Rosenthal, D.: Therapeutic ultrasound in the treatment of glaucoma. I. Experimental model. Ophthalmology 92:339, 1985.

4. Coleman, D. J., Lizzi, F. L., Driller, J., Rosado, A., Burgess, S. E. P., Torpey, J. H., Smith, M. E., Silverman, R. H., Yablonski, M. E., Chang, S., and Rondeau, M. E.: Therapeutic ultrasound in the treatment of glaucoma. II. Clinical applications. Ophthalmology 92:347, 1985.

5. Burgess, S. E. P., Silverman, R. H., Coleman, D. J., Yablonski, M. E., Lizzi, F. L., Driller, J., Rosado, A., and Dennis, P. H.: Treatment of glaucoma with high-intensity focused ultrasound. Ophthalmology 93:831, 1986.

6. Coleman, D. J., Lizzi, F. L., Silverman, R. H., Dennis, P. H., Driller, J., Rosado, A., and Iwamoto, T.: Therapeutic ultrasound. Ultrasound Med. Biol. 12:633, 1986.

7. Coleman, D. J., Silverman, R. H., Yablonski, M. E., Harmon, G. K., and Lucas, B. C.: Ultrasonic treatment of glaucoma. In Spaeth, G. L., Katz, L. J., and Parker, K. W. (eds.): Current Therapy in Glaucoma Surgery. Philadelphia, B. C. Decker, 1989, pp. 205–208.

8. Maskin, S. L., Mandell, A. I., Smith, J. A., Wood, R. C., and Terry, S. A.: Therapeutic ultrasound for refractory glaucoma. A three center study. Ophthalmic Surg. 20:186, 1989.

9. Lizzi, F. L., Driller, J., Ostromogilsky, M., and Coleman, D. J.: Thermal model for ultrasonic treatment of glaucoma. Ultrasound Med. Biol. 10:289, 1984.

10. McDonnell, P. J., Quigley, H. A., and Green, W. R.: Effect of therapeutic ultrasound on intraocular lenses. Ophthalmic Surg. 17:655, 1986.

11. Burgess, S. E. P., Iwamoto, T., Coleman, D. J., Lizzi, F. L., Driller, J., and Rosado, A.: Histologic changes in porcine eyes treated with high-intensity focused ultrasound. Ann. Ophthalmol. 19:133, 1987.

12. Schubert, H. D., and Federman, J. L.: The role of inflammation in CW Nd:YAG contact transscleral photocoagulation and cryopexy. Invest. Ophthalmol. Vis. Sci. 30:543, 1989.

13. Yablonski, M., Masonson, H. N., El-Sayyad, F., Dennis, P. H., Hargrave, S., and Coleman, D. J.: Use of therapeutic ultrasound to restore failed trabeculectomies. Am. J. Ophthalmol. 103:492, 1987.

14. Devenyi, R. G., Trope, G. E., Hunter, W. H., and Badeeb, O.: Neodymium:YAG transscleral cyclocoagulation in human eyes. Ophthalmology 94:1519, 1987.

15. Klapper, R. M., Wandel, T., Donnenfeld, E., and Perry, H. D.: Transscleral neodymium:YAG thermal cyclophotocoagulation in refractory glaucoma. A preliminary report. Ophthalmology 95:719, 1988.

16. Badeeb, O., Trope, G. E., and Mortimer, C.: Short-term effects of neodymium-YAG transscleral cyclocoagulation in patients with uncontrolled glaucoma. Br. J. Ophthalmol. 72:615, 1988.

17. Hampton, C., Shields, M. B., Miller, K. N., and Blasini, M.: Evaluation of a protocol for transscleral neodymium:YAG cyclophotocoagulation in one hundred patients. Ophthalmology 97:910, 1990.

18. Valtot, F., Kopel, J., and Haut, J.: Treatment of glaucoma with high intensity focused ultrasound. Int. Ophthalmol. 13:167, 1989.

19. Stenk, C. C., v.d. Valk, P. H. M., van Hees, C. L. M., van Delft, J. L., van Best, J. A., and Oosterhuis, J. A.: The effect of therapeutic ultrasound on the average of multiple intraocular pressures throughout the day in therapy-resistant glaucoma. Graefes Arch. Clin. Exp. Ophthalmol. 227:36, 1989.

OPHTHALMIC MINIATURE

That is also why I tend, unjustly, to be impatient with social scientists, who struggle to make sense of large bodies of observational and experimental data not yet reducible to neat little nuggets of knowledge. And it is also why in my own field I am not an eager seeker of information. I like to operate with only a fraction of the enormous accumulation of knowledge. When I open a new issue of a scientific journal I do not scan the table of contents looking for exciting novelty; on the contrary, I hope that here will be nothing in it that I must read. I once mentioned this fear of input to Al Hershey, who replied that everyone felt more or less as I did, but I was the only one arrogant enough to admit it. Maybe so.

S. E. Luria, *A Slot Machine, A Broken Test Tube*
New York, Harper & Row, 1984, p. 115

A Physical Analysis of the Factors That Determine the Contour of the Iris

James S. Tiedeman, M.D.

By solving equations that result from the application of basic newtonian physical principles, I developed a model that can predict the profile of the iris by using only the pupil radius, the iris root radius, and the anterior displacement of the pupil from the iris root. The model requires some theoretically and clinically reasonable assumptions regarding the relative importance of forces acting on the iris. Former analyses made false assumptions about contact between the lens and the iris, as well as inappropriate substitution of the physical concept of force for tension. The validity of the new model and its inherent assumptions can now be tested with biometric measurements made in normal eyes and eyes with shallow anterior chambers.

THE CONTOUR OF THE IRIS as it relates to the phenomenon of angle closure and the concept of pupillary block has been the subject of much interest and subjective description.[1-3] Attempts to describe the conditions physically and mathematically[4-8] have involved incorrect usage of the physical concepts of force (a vector quantity) and tension (a scalar quantity).

The model I developed starts with the fundamental concepts of newtonian physics together with some reasonable assumptions regarding the physical properties of iris tissue. These assumptions are that the iris is a pliable diaphragm of negligible thickness supported firmly only along its outside circumference (the iris root), and that the forces acting within and upon the iris are produced by the following: the radially oriented dilator muscle fibers; the iris sphincter muscle; hydrostatic pressure acting from behind the iris (P_{pc}); hydrostatic pressure acting from in front of the iris (P_{ac}); and the force exerted upon the iris root keeping it anchored in position. The model further assumes that there is no force of interaction between adjacent dilator fibers (elastic coupling) within the substance of the iris, and that there is axial symmetry about a line normal to the pupillary plane through the center of the pupil.

Material and Methods

To understand the model it is first necessary to understand the concept of a pressure relief valve (Fig. 1). This valve is simply a flap large enough to cover completely an opening of area A and held closed by a spring exerting a (vector) force F, keeping the flap in the closed position. If a fluid enters the chamber, the

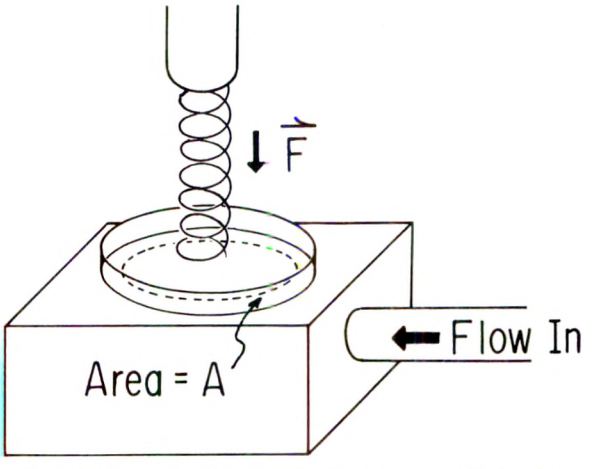


Fig. 1 (Tiedeman). Model of pressure relief valve. Fluid enters the chamber and is released when the pressure reaches that required to lift occluding cover, allowing escape of fluid.

Accepted for publication Nov. 29, 1990.

From the Department of Ophthalmology, Duke University Medical Center, Durham, North Carolina.

Reprint requests to James S. Tiedeman, M.D., Department of Ophthalmology, Duke University Medical Center, Box 3802, Durham, NC 27710.

pressure (P) will increase. There will be no escape of fluid, however, until P = F/A. When the pressure reaches this value the occluding flap can open and allow fluid to escape. As long as the rate of fluid flow is low the pressure in the chamber will be maintained at P = F/A.

In a similar fashion the pressure in the posterior chamber is determined by iris forces. The pressure in that compartment will be only the amount required to lift the iris gently off the anterior lens surface, allowing escape of aqueous from the posterior chamber into the anterior chamber around the pupillary margin. Note that the lens itself is not in contact with the iris and exerts no direct force on it under normal circumstances. Across the entire surface of the iris there is a pressure difference (P) between the posterior and anterior chamber, $P = P_{pc} - P_{ac}$.

Consider now a unit segment of iris that will be defined as a wedge of tissue including a dilator muscle fiber and a sector of iris sphincter (Fig. 2). Let a = radius of pupil; b = radius of iris root; and z = anterior displacement of the plane of the pupil from the plane of the iris root. Define ρ as the number of such segments per radian of iris. Looking at one such unit segment in cross section (Fig. 3), define t as the tension exerted by the dilator muscle fiber. Note that this tension must be uniform along the entire strip and therefore exerts the same pull at both ends. At the pupillary margin the tension (t) is balanced by the pupillary sphincter muscle, which acts to pull only in a radial direction (with no anteriorly or posteriorly directed components). At the other end of the strip a force is exerted by the iris root as a vector quantity, f, with the same magnitude as t and in the direction of the angle of iris takeoff from the iris root. Define the angle of iris takeoff as Θ.

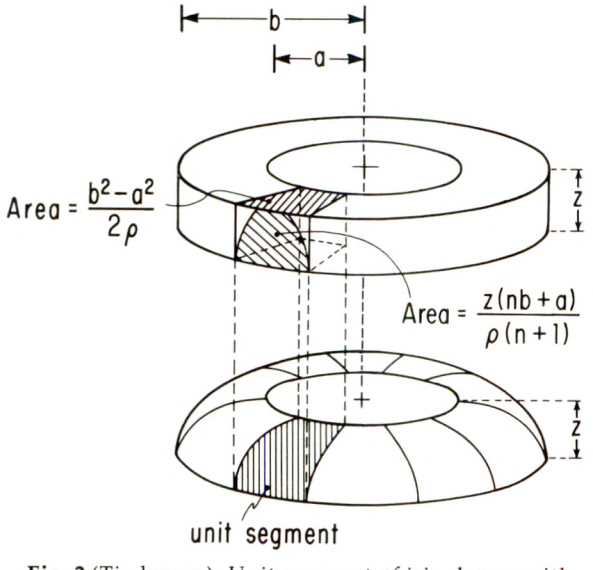


Fig. 2 (Tiedeman). Unit segment of iris shown with projection of area in anterior and radial directions.

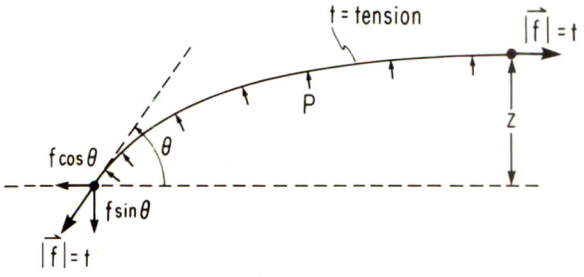


Fig. 3 (Tiedeman). Cross section of iris unit segment showing forces acting at the end points and pressure acting along the length of the segment.

The force supplied by the iris root can be resolved into an anteroposterior component equal to f sin Θ, and a radial component f cos Θ. The anterior force acting on the unit strip is the pressure, P, times the equivalent frontal area of the iris, $(b^2 - a^2)/2\rho$. Note that this area is independent of the actual contour of the iris (Fig. 2). Therefore,

$$f \sin \Theta = P(b^2 - a^2)/2\rho \quad (1)$$

Similarly, the radial component of force is P (pressure) multiplied by the equivalent surface area projected in a radial direction (Fig. 2). This projection is complicated because the equivalent area is dependent upon the shape of the iris contour. For the purpose of calculating the radially projected area only, the model makes the initial assumption that the shape is closely, but not ideally, approximated by a function of the form,

$$y = z - z[(r-a)/(b-a)]^n \quad (2)$$

Define y as the anterior displacement from the iris root plane of a point along the iris contour and r as the radial distance of that point from the center of the pupil. The equation describes a parabola when n = 2, a straight line when n = 1, and the like. The radially projected area then becomes

$$A = z(nb + a)/\rho(n + 1) \quad (3)$$

The radial component of force at the iris root (f cos Θ) must therefore equal the radially directed force caused by pressure, P, minus the force

acting in the opposite direction supplied by the iris sphincter muscle, which gives

$$f \cos \Theta = [Pz(nb + a)/\rho(n + 1)] - f \quad (4)$$

The Pythagorean theorem gives

$$f^2 \sin^2 \Theta + f^2 \cos^2 \Theta = f^2 \quad (5)$$

Squaring Equations 1 and 4 and substituting into Equation 5 yields

$$P = \frac{8\rho fz(n+1)(nb+a)}{[(n+1)^2(b^2-a^2)^2+4z^2(nb+a)^2]} \quad (6)$$

Substituting this quantity for P into Equation 1 gives

$$\sin \Theta = \frac{4z(n+1)(nb+a)(b^2-a^2)}{(n+1)^2(b^2-a^2)^2+4z^2(nb+a)^2} \quad (7)$$

or

$$\Theta = \sin^{-1}\left[\frac{4z(n+1)(nb+a)(b^2-a^2)}{(n+1)^2(b^2-a^2)^2+4z^2(nb+a)^2}\right] \quad (8)$$

Note that this angle depends only upon the pupillary radius (a), the iris root radius (b), the anterior displacement of the pupil (z), and the value of n, but does not depend upon ρ or P.

Because Θ in Equation 8 is dependent upon n (from the approximation to the iris contour made in Equation 2), it is not solvable in closed form since n must also ultimately depend upon Θ. Because Θ is not strongly dependent upon n, it is possible to start with an arbitrary n and calculate a first approximation to Θ. That approximate Θ can then be used to determine a new and more nearly correct value of n because from Equation 2, when r = b,

$$\Theta = \arctan |dy/dr| = \arctan (nz) \quad (9)$$

or

$$n = (\tan \Theta)/z$$

The calculation can be repeated using the newly calculated n to yield a more precise second approximation. With computer iteration, this process is repeated until the unique solution that satisfies the condition of n in Equation 2 predicting the same angle Θ as Equation 8 is calculated. The entire iris profile can be predicted in a second series of iterative steps. Once the angle Θ is found, a small change in radial position, δ, can be multiplied times the tangent of the angle Θ to obtain a new set of starting coordinates. The new angle Θ in this position can be found and the entire cross section can be calculated in stepwise fashion with a high precision if δ is kept suitably small.

That the angle Θ is independent of P may not be intuitively obvious, but it is mathematically predictable. For example, if the pupil remains the same size while the dilator and sphincter muscles both increase their respective tones by a factor of two, the effect on pressure, P, must also be a first order one. P would therefore increase by a factor of two and the contour would not change. The iris contour in the unique case of a peripheral surgical iris coloboma is not predicted by the model, because in that case there is no pressure difference, P, between posterior and anterior chamber, and the iris rests directly on the lens surface and assumes a straight line from its most peripheral point of contact with the lens to the iris root. This theoretical prediction has been observed empirically.[9]

Results

To calculate the complete iris contour, I wrote a computer program in IBM BASIC to perform the two necessary independent iterative approximations. The program starts with an arbitrary n and then calculates Θ using Equation 8. It then compares the angle Θ with that of the simple contour of Equation 2 and increases n in incremental steps until these angles are equal. The assumption is then made that this is an extremely close approximation to the actual curve at this location, and the first iteration stops.

The angle of tangency to the iris surface at any point along the iris contour can be calculated using that point as the new coordinate of a presumed iris root equivalent. The program starts at r = b and calculates Θ. It then makes a small increment, δ, in r and calculates the y coordinate at the end of that increment as

$$y = y_0 + \delta \tan \Theta \quad (10)$$

Define y_0 as the starting value of y. The new r and y coordinates at the end of this increment become the new iris root equivalent, and the process is repeated until r = a.

To check the validity of the approximations inherent in using steps of finite size, the program can be run with any increment in r being chosen. The calculated coordinates actually obtained differ by only a few parts in 10^3 if increments of one-thousandth of radius b are compared with steps one-tenth smaller.

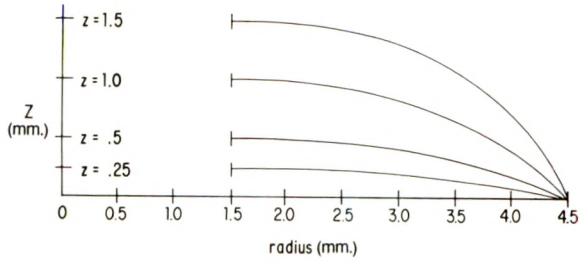


Fig. 4 (Tiedeman). Representative iris contours with the iris root insertion at 4.5 mm, a 1.5-mm pupil radius, and various anterior displacements of the pupillary plane.

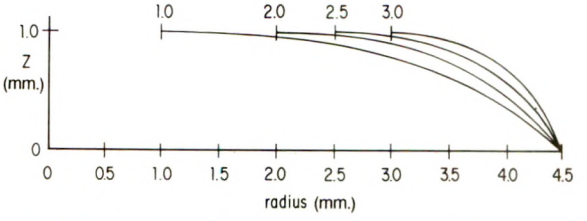


Fig. 5 (Tiedeman). Representative iris contours given a fixed anterior pupil displacement of 1.0 mm, the iris insertion at 4.5 mm, and various pupil diameters.

Figure 4 depicts a family of iris contour curves obtained by holding constant the values of pupil radius (a) and iris root radius (b) and varying the anterior displacement of the pupil (z). Another family of curves is shown in Figure 5. The iris root radius (b) and anterior displacement of the pupil (z) are kept constant, and the pupillary radius (a) is varied.

Discussion

Previous attempts to analyze mathematically[4,7] the factors that determine the degree of relative pupillary block have made serious errors in physical principles. These errors invalidate the conceptual arguments set forth. Mapstone[4] described what he incorrectly called a force along the dilator muscle. Force is a vector quantity acting at a point, having magnitude and direction. What he described is more correctly termed tension along the dilator muscle. Tension along a contour cannot be resolved into simple components connecting the end points, as his analysis incorrectly attempted to do.

My model does not specifically attempt to solve for the difference in pressure between the posterior chamber and the anterior chamber, inherently linked to the concept of pupillary block. Indeed, there is in all physiologic configurations of the normal anterior chamber a degree of blockage of flow from the posterior to the anterior chamber. This block or resistance to flow will certainly be greater at any given pupil size if the contractions of the sphincter and dilator muscles are increased. However, as long as the force acting between fibers (that is, the elasticity of the iris stroma) is negligible compared to that exerted by the muscles, only pupillary size and anterior displacement of the pupil will uniquely define the contour of the iris surface. To the extent that this assumption is not valid, this model would predict a greater bowing forward of the iris than actually occurs. This error would be most significant at those places with the smallest predicted radius of curvature of the surface, because it is at these places that the adjacent dilator fibers would be most separated and the interfiber or stromal elasticity would be most significant. The more peripheral iris points would therefore be predicted as more anteriorly displaced than their true position. The magnitude of the error would be less if the sphincter and dilator tones were increased at a given pupil radius.

Another difficulty in actually verifying the validity of the model is that the iris is not the infinitely thin surface it is assumed to be in the calculations. There is greater thickness near the pupillary margin caused by the sphincter muscle that must be taken into account.

This model relates directly to the clinical situation of angle closure. If the angle that the trabecular meshwork makes with the plane of the anatomic angle of the eye is less than the angle of takeoff of the iris from the iris root (angle Θ), the trabecular meshwork would be occluded by the iris. This occurs with greater likelihood for greater values of z at any pupil size (Fig. 4). The effect of dilation for a fixed value of z is that increasing dilation will always increase Θ (Fig. 5). It must be kept in mind, however, that because of the anterior lens surface contour, the distance z decreases as the pupil dilates. If the decrease in z that occurs with increasing pupil diameter is taken into account, the model predicts that the mid-dilated pupil will produce the largest Θ. Figure 6 depicts a hypothetic anterior lens surface contour and three different pupillary sizes. At each pupillary radius the computer routine was used to generate the resultant iris contour, and these

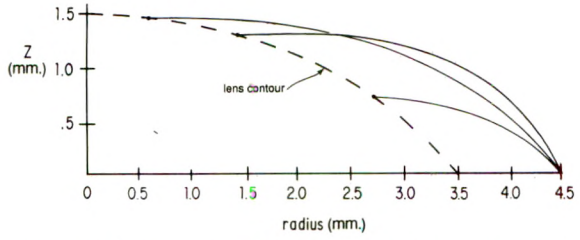


Fig. 6 (Tiedeman). Representative iris contours at three pupil diameters when the anterior displacement of the pupil is determined by the lens contour. The steepness of insertion at the iris root (angle Θ) is greatest for the mid-dilated pupil.

contours are plotted. It becomes apparent, therefore, that in the shallow anterior chamber the greatest risk of angle closure is correctly predicted to occur in mid-dilation.

BASIC computer program—This program, written in IBM BASIC (Fig. 7), first requests input of the parameters a (pupil radius), b (iris root radius), z (anterior displacement of the pupil plane from the iris root plane), and n (an arbitrary starting point for the calculation) in lines 10 through 421. It then calculates the angle THETA using Equation 8 (lines 501 through 585) and compares the calculated THE-

```
1 LPRINT
2 LPRINT
3 LPRINT
4 C = 100
10 PRINT "n=";
20 INPUT N#
25 LPRINT "n= "N#
100 PRINT "a=";
200 INPUT A#
250 LPRINT "a= "A#
300 PRINT "b=";
400 INPUT B#
405 LPRINT "b= "B#
410 PRINT "z=";
420 INPUT Z#
421 LPRINT "z= "Z#
422 KEEP = N#
500 PRINT "N=" N#
501 TOP# = 4#*(N#+1#)*(N#*B#+A#)*(B#*B#-A#*A#)*Z#
502 BOT# = (N#+1#)*(N#+1#)*(B#*B#-A#*A#)*(B#*B#-A#*A#)+4#*Z#*Z#*(N#*B#+A#)*(N#*B
#+A#)
553 SINE#=TOP#/BOT#
560 COSSQ#=1#-SINE#*SINE#
570 COSI#=SQR(COSSQ#)
580 TANG#=SINE#/COSI#
585 THETA#=ATN(TANG#)*45#/ATN(1#)
900 PRINT "theta =" THETA#;
910 PRINT "b= " B#;
920 PRINT "z= " Z#
921 TEST#=ATN((N#*Z#)/(B#-A#))*45#/ATN(1#)
922 PRINT "TEST=" TEST#
923 IF TEST#<THETA# THEN GOTO 7000
924 IF C<10 GOTO 999
950 LPRINT "R= "B#;
951 LPRINT "z= "Z#;
952 LPRINT "theta ="THETA#;
953 LPRINT "n= "N#
954 C=0
999 C=C+1
1000 B#=B#-(.1#)
1050 IF B#<A# THEN STOP
1100 Z#=Z#-.1#*TANG#
1200 N# = KEEP
1250 GOTO 500
7000 N# = N#+.1#
12000 GOTO 500
```

Fig. 7 (Tiedeman). Computer program written in IBM BASIC used to calculate iris contour.

TA with the slope of Equation 2 (TEST) as determined from the value of n. If TEST< THETA the value of n is then raised in fixed increments, the size of which are specified in line 7000. Once the two are equal this iteration stops and the value of THETA is established for the starting point (the iris root).

The next starting point, or iris root equivalent, is a decrease from the starting b by the increment specified in line 1000. Similarly, a new z must then be calculated for this new starting point. The decrement in z is equal to the incremental change in b times the tangent of angle THETA. The new z is then calculated in line 1100. This initial iteration is then carried out for the new starting point until the angle THETA associated with that point is determined.

Because there can be thousands of such points calculated, a skip routine is incorporated to economize printout paper and allows every tenth or hundredth or any number of skipped calculations between printed outputs. The skip interval is chosen in line 924.

All calculations are made in double precision and the BASIC/D option must be chosen at startup of the BASIC mode.

References

1. Chandler, P. A.: Narrow-angle glaucoma. Arch. Ophthalmol. 47:695, 1952.
2. Barkan, O.: Etiology of narrow-angle glaucoma. Am. J. Ophthalmol. 36:901, 1953.
3. ———: Narrow angle glaucoma. Pupillary block and the narrow-angle mechanism. Am. J. Ophthalmol. 37:332, 1954.
4. Mapstone, R.: Mechanics of pupil block. Br. J. Ophthalmol. 52:19, 1968.
5. ———: Closed-angle glaucoma. Theoretical considerations. Br. J. Ophthalmol. 58:36, 1974.
6. Aviner, Z.: Pupil-block. Its mechanism and prevention. Ophthalmologica 163:273, 1971.
7. Kondo, T., and Miura, M.: Mathematical analysis of pupillary block. Glaucoma 11:176, 1989.
8. Lowe, R. F.: Angle closure, pupil dilatation, and pupil block. Br. J. Ophthalmol. 50:385, 1966.
9. Jin, J. C., and Anderson, D. R.: The effect of iridotomy on iris contour. Am. J. Ophthalmol. 110:260, 1990.

OPHTHALMIC MINIATURE

His left eye closed involuntarily, a twitch that had developed when he was eight years old and afraid of horses, something his father did not condone. She watched, fascinated, as the eyelid slowly opened again and his pupil readjusted itself after a momentary wandering.

Elizabeth Winthrop, *In My Mother's House*
New York, New American Library, 1989, p. 40

The Physiologic Characteristics of Relative Pupillary Block

Douglas R. Anderson, M.D., Jai Chi Jin, M.D., and Martha M. Wright, M.D.

In biometric photographs of 13 patients, we quantified the iris contour in eyes with central anterior chamber depths ranging from 1.9 to 3.4 mm (epithelium to lens surface). This actual profile was compared to that predicted by a theoretical analysis of the forces acting on the iris. The average discrepancy between the calculated actual and the theoretically predicted iris position was only −0.01 to +0.03 mm. The close agreement validates the model under normal conditions and in the presence of relative (nonsynechial) pupillary block. The theoretical iris shape may not occur under conditions that violate the underlying physical assumptions of the mathematical model, such as when iridectomy eliminates the pressure difference between the anterior and posterior chamber or when synechiae introduce additional forces on the iris other than the ones included in the analysis.

TO WHATEVER DEGREE there is resistance to flow of aqueous humor through the space between the iris and lens (relative pupillary block), a pressure difference develops between the posterior and anterior chambers. The pressure difference lifts the iris off the lens surface, which allows aqueous flow sufficient to produce a balance between the increased posterior chamber pressure and the resistance to flow into the pupillary passage.

From basic physical principles, Tiedeman[1] constructed a mathematical model of this equilibrium condition. Although the anterior bulge in the iris contour is produced by the posterior chamber pressure balancing the iris sphincter tone, a consequence of the model is that once these forces have determined the pupil margin plane at equilibrium, the iris contour can be calculated without knowing either the sphincter tone or the transchamber pressure difference. The contour in an iris sector is constrained to a predictable shape, by a given position of the iris root attachment and the pupil margin, in relation to each other and in relation to the pupillary axis.

We developed a biometric method that allowed a true optical cross section of the anterior chamber to be obtained by correcting a photographic image for the displacement effects caused by viewing the iris through the cornea.[2] We compared our calculated actual iris position to the theoretical position predicted from Tiedeman's model in 13 patients. Two patients had normal eyes with relatively flat iris contours. The other 11 patients with centrally shallow anterior chambers and narrow or closed anterior chamber angles were studied to offer the greatest challenge to the validity of the model. The close agreement that we found serves both to confirm the accuracy of our optical correction method and the applicability of Tiedeman's mathematical model to living human eyes.

Subjects and Methods

We studied 11 patients with narrow anterior chamber angles in association with shallow anterior chambers. We also studied two subjects with normal eyes. The study protocol was approved in advance by the University of Miami Institutional Review Board. All subjects documented in writing that they consented to participate after being informed about the nature of the study. Biometric photographs were taken in a manner described previously.[2] In brief, optical cross sections of eight anterior segment meridians were photographed with a rotating slit-lamp camera that used the Scheimpflug principle to focus the entire length of the slit beam on the film plane. Correction of the image was made to compensate for the distortion produced by the tilted film plane and

Accepted for publication Nov. 6, 1990.

From the Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida. This study was supported in part by National Glaucoma Research, a program of American Health Assistance Foundation, Rockville, Maryland and by the U.S. Public Health Service core center grant P30-EY-02180 and National Research Service Award T32-EY-07021 from the National Institutes of Health.

Reprint requests to Douglas R. Anderson, M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

for the optical effect of the cornea with a slightly simpler procedure[3] than the one used in the original description.[2]

Some of the subjects were also included in a report comparing iris contour before and after iridotomy,[3] but in the present study only images obtained before iridotomy were used. Additional subjects with narrow angles had not been part of the previous study and only had photographs taken before an iridotomy. Two other subjects with normal anterior chamber depths were recruited. They had no previous ocular abnormality or evidence of abnormality on a clinical examination that included visual acuity determination, tonometry, biomicroscopy, and ophthalmoscopy.

The output of the computerized analysis was a quantified representation of the cross section of the anterior chamber with the corneal apex at the origin of the coordinate system. On the printout, the scale was such that 0.5 inch represented 1 mm (×12.7 enlargement). To satisfy the condition that the direction of the iris sphincter force must be parallel to the abscissa, the computer-corrected images were traced (smoothing any minor irregularities in the iris surface), and a new coordinate system was established with the abscissa tangent to the upper surface of the iris at the most anterior point on the two leaves of the iris in the optical cross section (Fig. 1). The origin was placed on the abscissa at the center of the pupil, and the ordinate was placed perpendicular to the abscissa at the origin. On the tracing the most peripheral point (point B) on the visualized iris, at or near its root, was identified. The distance z was measured from point B to the abscissa, and the distance b from point B to the ordinate. The distance from the ordinate to the edge of the pupil (point A) was measured as distance a. All distances were measured parallel to the axes and were assigned a positive sign.

From each subject we selected two meridians with technically adequate images, which gave us 28 sections for analysis. From the measured values of a, b, and z, the x, y coordinates of the iris contour were calculated in 0.02-mm steps horizontally (with every tenth value printed out), starting at the iris root (point B, coordinate b, z) and ending at the pupil margin (point A, coordinate a, 0). The calculation was achieved by means of the computer program devised by Tiedeman.[1] In this program, the exponent n is found at each point by computerized iteration in 0.02 steps until the conditions of two equations in Tiedeman's model are satisfied simultaneously. The slope of the function at that point was used to determine the y coordinate of the next point 0.02 mm closer to the pupil, and the process was repeated.

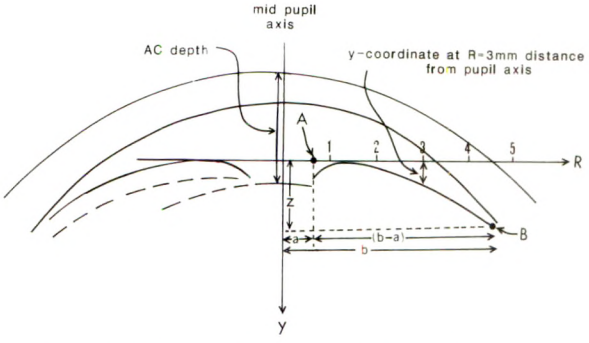


Fig. 1 (Anderson, Jin, and Wright). Diagram of coordinate system for distance y vs radial distance R, superimposed on an optical cross section of the anterior chamber. On the left, the presumed locations of the posterior iris surface and lens surface behind the iris are shown as a dotted line. On the right, only the anterior iris and lens surfaces, as seen in the photograph, are drawn. The position of points A (extrapolated pupil margin) and B (iris root) are indicated, as well as the distances a, b, and z. (AC indicates anterior chamber.)

The y coordinates theoretically predicted were tabulated for the points nearest to 1, 2, 3, 4, and 5 mm from the pupillary axis. At corresponding distances from the pupillary axis, the actual iris position was measured to the nearest 64th of an inch (corresponding to 0.03125 mm of iris position) with a ruler marked in 32nds of the inch. The measurement was made without knowledge of the predicted y coordinate. This measured actual position was compared to the position predicted by Tiedeman's model.

Results

As a typical example, Figure 2 shows the close agreement between the observed actual iris contour and the predicted iris position in a patient with a shallow anterior chamber. As shown, the actual iris position was, on the average, slightly more anterior than predicted 2 mm from the pupil but somewhat more posterior than predicted further toward the periphery. Figure 3 shows the iris contour of an individual with normal anterior chamber depth.

As displayed in Table 1, the difference be-

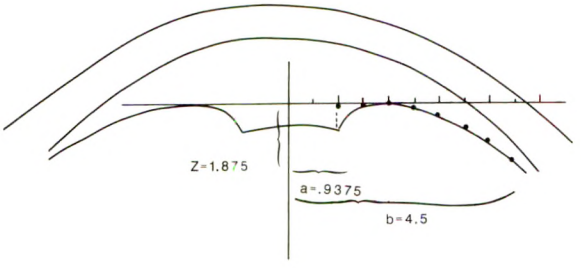


Fig. 2 (Anderson, Jin, and Wright). Example from an eye with narrow angles, showing the close agreement of predicted iris position (dots) with the actual iris position.

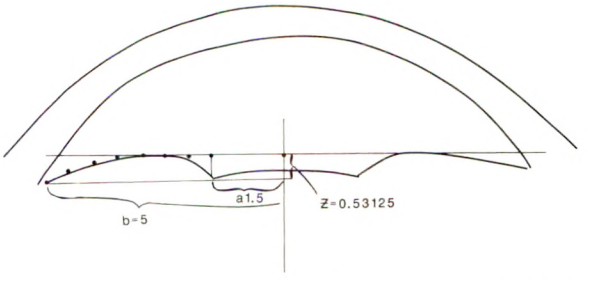


Fig. 3 (Anderson, Jin, and Wright). Example from a normal eye with a deep anterior chamber. The predicted iris position (dots) nearly coincides with the actual iris contour.

tween actual and predicted iris position was small. Even assuming that the two meridians that were used from each individual were independent observations, the discrepancy was not statistically significant overall, except at a radial distance of 2 mm where the iris surface was on the average 11 μm (about the diameter of a white blood cell) more anterior than predicted. Although the discrepancy was small and overall not statistically significant, there was an orderly increase in the discrepancy toward the periphery. This tendency was statistically significant by repeated-measures analysis of variance with orthogonal polynomial test of linear trend[4] ($P = .02$).

In the midregion, but not at the ends where iris position was given, there was also an orderly increase in the discrepancy with increase in the value for z (the distance between the plane of the pupil and the plane of the iris root), shown by a statistically significant correlation coefficient (Table 2). The discrepancy correlated as well with the ratio, $z/(b-a)$ (Table 3). Although the distance z was greater in eyes with smaller anterior chamber depths ($r = -.6$, $P < .001$), the negative correlation between the anterior chamber depth and the actual and theoretical discrepancy in the midregion was not statistically significant (Table 4).

For comparison with the Tiedeman formulation, we examined how closely a simple parabola would approximate the iris contour. With the formula $y(R) = (z)(R-a)^2/(b-a)^2$ to determine the y coordinate at radial distance R, we computed the parabola that had its vertex at the extrapolated pupil margin (point A) and passed through the iris root (point B). The parabolic approximation was posterior to the actual iris surface by a statistically significant amount (Table 5), and the discrepancy was larger than the discrepancy with the Tiedeman model (Table 1). Although the parabolic approximation was still close, with a discrepancy that may be small enough for some purposes, the Tiedeman prediction and the parabolic estimation were significantly statistically different from one another at all locations (Table 6). There might have been an error in measuring the actual iris

TABLE 1

ACTUAL Y COORDINATE AND Y COORDINATE OF IRIS POSITION PREDICTED BY TIEDEMAN MODEL (mm)

		Y COORDINATE		DISCREPANCY				RANGE	
R*	N	ACTUAL (MEAN)	PREDICTED (MEAN)	MEAN	S.E.†	P‡	MEDIAN	MINIMUM	MAXIMUM
1	11	.0028	.0020	.0009	.003	.760	−.001	−0.010	0.030
2	26	.0180	.0288	−.0108	.005	.025	−.009	−0.040	0.060
3	26	.1707	.1572	.0135	.012	.291	.002	−0.100	0.130
4	25	.4775	.4537	.0238	.012	.057	.031	−0.080	0.140
5	4	.6641	.6298	.0343	.045	.503	−.001	−0.003	0.170

*Radial distance from pupillary axis (mm).

†Standard error of the mean discrepancy.

‡Two-tailed paired *t*-test.

TABLE 2
CORRELATIONS OF DISCREPANCY* WITH z

R†	N	r‡	ONE-TAILED PROBABILITY
1	11	.2424	NS§
2	26	−.1676	NS
3	26	.5731	<.01
4	25	.5155	<.01
5	4	.8689	NS

*Difference between actual and predicted iris position.
†Radial distance from pupillary axis (mm).
‡Correlation coefficient.
§NS indicates not significant.

TABLE 3
CORRELATIONS OF DISCREPANCY* WITH THE RATIO z/(B − A)

R†	N	r‡	ONE-TAILED PROBABILITY
1	11	.2179	NS§
2	26	−.1879	NS
3	26	.5686	<.01
4	25	.5525	<.01
5	4	.7555	NS

*Difference between actual and predicted iris position.
†Radial distance from pupillary axis (mm).
‡Correlation coefficient.
§NS indicates not significant.

position, which was common to both discrepancies, because there was a strong correlation between the two discrepancies ($r = .61$ to $.99$ at various radial distances, $P < .001$) for all distances.

Discussion

The actual and predicted contours coincided almost to the degree to which iris position can be measured with the methods used. On the tracings produced by the computer after correction for the optics of the camera and the cornea, the scale is 0.5 inch = 1 mm. With a ruler marked in 32nds of an inch, we could measure the distances of the iris from the abscissa to the nearest 1/64th of an inch, corresponding to 0.03 mm (30 μm). An average discrepancy less than this amount represents a remarkably close fit of the calculated actual iris position and the theoretical predicted contour of the iris. This congruity of the profiles mutually confirms the biometric calculations used to determine actual iris contour and the theoretical model that predicts the contour from basic physical principles.

The biometric method has previously been tested for reproducibility,[2] but its accuracy has been confirmed only at the center of the anterior chamber, the only location at which there is an independent measure of the position of an intraocular tissue surface in the living eye.[3] Our present data show that all along the iris meridian, the calculated iris position conforms to theoretical expectations, without an evident error in the optical calculations used to determine the actual iris surface position from the photographic image.

Conversely, the mathematical model of relative pupillary block accurately predicts the observed actual iris shape in the 13 subjects stud-

TABLE 4
CORRELATIONS OF DISCREPANCY* WITH ANTERIOR CHAMBER DEPTH

R†	N	r‡	ONE-TAILED PROBABILITY
1	11	.0995	NS§
2	26	.0548	NS
3	26	−.3719	NS
4	25	−.2057	NS
5	4	−.9123	NS

*Difference between actual and predicted iris position.
†Radial distance from pupillary axis (mm).
‡Correlation coefficient.
§NS indicates not significant.

TABLE 5
ACTUAL Y COORDINATE AND Y COORDINATE OF IRIS POSITION PREDICTED BY PARABOLIC FORMULA (mm)

		Y COORDINATE		DISCREPANCY		
R*	N	ACTUAL (MEAN)	PREDICTED (MEAN)	MEAN	S.E.†	P‡
1	11	.0028	.0060	−.0031	.004	.416
2	26	.0180	.0554	−.0373	.006	<.001
3	26	.1707	.2277	−.0570	.010	<.001
4	25	.4775	.5214	−.0438	.010	<.001
5	4	.6641	.6649	−.0008	.037	.984

*Radial distance from pupillary axis (mm).
†Standard error of the mean discrepancy.
‡Two-tailed paired *t*-test.

TABLE 6

COMPARISON OF DISCREPANCY OF ACTUAL IRIS Y COORDINATE WITH THE Y COORDINATE OF THE TIEDEMAN PHYSICAL MODEL AND THE Y COORDINATE OF THE PARABOLIC ESTIMATION

		Y COORDINATE		DIFFERENCE BETWEEN DISCREPANCIES		
R*	N	DISCREPANCY (MODEL)	DISCREPANCY (PARABOLA)	MEAN	S.E.†	P‡
1	11	.0009	−.0031	.0040	.002	.068
2	26	−.0108	−.0373	.0266	.005	<.001
3	26	.0135	−.0570	.0705	.008	<.001
4	25	.0238	−.0438	.0676	.007	<.001
5	4	.0343	−.0008	.0351	.008	.024

*Radial distance from pupillary axis (mm).

†Standard error of the mean difference between discrepancies.

‡Two-tailed paired *t*-test.

ied. The iris contour was approximated reasonably well by a second-order polynomial (parabola), but the curve based on presumed physiologic circumstances in Tiedeman's formulation provided an even better fit (Table 6). This serves to verify the applicability of the physical principles embodied in the mathematical model to actual anatomic and physiologic circumstances in the living human eye.

A seeming paradox of the model is that changes in the sphincter tone, dilator tone, or posterior chamber pressure (in response to the tightness of fit of the iris against the lens) may not affect the iris contour. The mathematical model predicts that once these forces produce an equilibrium condition with a given position of the pupil relative to the iris root, the contour will be the same no matter what combination of forces are at play to produce that pupil position. For example, simultaneous tightening of the sphincter and dilator muscles (such that the pupil diameter is unchanged) will result in a higher tension along the iris and a higher pressure within the posterior chamber. At equilibrium, the pupil margin may move backward slightly (to narrow the channel and account for a higher posterior chamber pressure), but with only a slight change in pupil position the model would predict only a small change in iris contour.

The applicability holds only when the pressure flow relationships are at equilibrium and all the assumptions of the physical mathematical model are met. These need to be considered, both to see how well the assumptions are met in our particular group of 13 subjects and to know the limits of the general application to other individuals.

One assumption is that the behavior of the iris (a structure with finite, variable thickness and inhomogeneous composition) can for analytic purposes be reduced to a thin membrane. (It need not incidentally be of homogeneous elasticity along its entire radial length. In such a case, however, the violation of the assumption of absent lateral interaction becomes important, unless adjacent sectors are uniform.) If it is assumed that the iris stroma is loose and the main tautness of the iris resides in the dilator muscle layer, it is really the contour of that layer, near the posterior surface, that the model represents. The visible layer is the anterior iris surface, and we assumed that it was parallel to the surface represented by the model, and thus of the same dimensions and shape. Realizing that we were studying not the anterior iris surface but a surface parallel to it, we made a smooth curve through the surface irregularities produced by the collarette of the iris or by corrugations of the surface. Additionally, in selecting point A (Fig. 1) we extrapolated the curve used for analysis of the anterior iris surface centrally toward the origin of the coordinate system rather than follow the rounded edge of the pupil margin posteriorly at the margin. In this way the actual curve was artificially kept parallel to the posterior iris surface all the way to the pupil margin. We used this smooth extrapolated curve, presumably parallel to the dilator muscle layer, as the actual contour that could be compared to the smooth theoretical curve. The smoothing necessary was minor in all cases and was always done before any of the theoretical calculations were performed.

The smoothed and extrapolated anterior iris surface is not perfectly parallel to the dilator muscle, because the iris is not of uniform thickness. The iris becomes thin near its root. This may in part account for a tendency for larger discrepancy between actual and theoretical in the periphery. (There are two additional components to the small error. Tiedeman[1] provided a theoretical reason for slightly anterior erroneous prediction in the periphery by his formulation. Additionally, the discrepancy is not measured normal to the surface at the periphery and is thus artificially exaggerated where the iris has a steep slope.) Similarly, the sphincter muscle makes the iris thicker in a region near the pupil, and this may account for the tenden-

cy for a discrepancy in the negative direction for points near the pupil. Yet, from these results, it appears that the anterior surface is sufficiently parallel to the dilator muscle that it can be taken as a close approximation of shape, unless there is an anatomic peculiarity (for example, localized iris atrophy or a tumor).

A second assumption of the mathematical model is that no force is derived from contact of the iris with the lens. The posterior surface of the iris is supported by the pressure of the posterior chamber, and near the pupil it is supported by pressure of the fluid in the channel between the posterior chamber and the anterior chamber. This support is disclosed when the posterior chamber pressure is relieved by iridotomy. The iris, having lost the support of the posterior chamber pressure, moves backward at the pupillary margin, as well as elsewhere.[3]

Thus, under natural conditions (without any iridotomy) the assumption is satisfied that the lens is not in contact with the iris and does not itself exert a force upon the iris. The lens has only the indirect effect of providing the posterior wall of the channel through which aqueous humor is flowing; its position simply helps determine the position the iris will assume under equilibrium conditions in which the resistance to flow into the pupil (related to the distance between the lens and iris) balances the anterior-posterior chamber pressure difference at a given flow rate.

The model assumes an equal pressure is exerted along the entire posterior iris surface, but this is true only to the degree that the channel between the iris and lens becomes critically narrow only at the pupil margin. With flow through a long narrow passage, the pressure supporting the iris might be expected to fall progressively as the pupil margin is approached. Evidently the resistance to flow into the anterior chamber is most marked at the pupil margin, such that the pressure supporting the peripupillary iris is not diminished enough to matter in the Tiedeman formulation, because the observed contour varies little from the theoretical shape. The actual shape of the passage is the gap between two curves: the anterior lens surface, which reaches its maximum anterior extent near the center of the pupil, and the nearly parabolic shape of the posterior iris surface, with its vertex at the pupil margin. These two curves approach each other at an angle that produces the narrowest passage at the pupil margin. An additional reason that the resistance is greatest at the pupil margin is that even with a uniform gap between lens and iris, the cross-sectional area of the annular channel would be at its least where the radius is the smallest.

Another assumption of the model is that each sector of the iris is free to stretch or move independently. This condition is not met, because adjacent sectors are attached to one another. Nonetheless, the contour is not affected if the elastic properties of adjacent sectors are identical. Despite some asymmetry of the iris at various meridians around the circumference, our results suggest that the difference between immediately adjacent sectors is small and has little influence on the contour in the usual iris.

Thus, it would appear that the assumptions of the mathematical model were satisfactorily met in the patients we studied. There are, however, conditions under which the model would not apply. For example, after iridotomy, there is no pressure difference between the posterior and anterior chambers, and in the absence of slack, the iris will be held in a straight line between its points of support. After iridotomy, the assumptions of the mathematical model are further violated by a lens-derived force that results when the iris is draped on the lens surface. The shape of the iris after iridotomy has been described previously.[3]

As an additional example, the model could not be expected to apply when there is blatant nonuniformity between adjacent sectors. For example, with a partial-thickness iridectomy, the pigment layer may bulge through the opening in the stroma. In this sector the contour obviously does not follow the smooth curve predicted by the mathematical model, and the bulge results because of restraints produced by adjacent sectors.

The mathematical model also does not apply when there are additional forces on the iris, for example from synechiae formation. Posterior synechiae of the iris to the lens produce a posteriorly directed force at or near the pupil, which permits the iris to bulge forward (iris bombé), so that the middle portion of the iris is more anterior than the pupillary margin. This anterior bulge cannot occur in the absence of a posterior synechia. Peripheral anterior synechiae also violate the assumption of the mathematical model, unless one considers that the effective iris root force is the sum of the force vector exerted by the anterior adhesion and the force vector generated by the posterior insertion into the ciliary body.

Similarly, the contour of the iris during indentation gonioscopy does not follow the theoretical mathematical model. At least three conditions of the model are violated: the pressure-flow-resistance relationships are not at equilibrium; there is contact between the lens and the iris at the pupil margin; and the posterior chamber pressure is not greater than the anterior chamber pressure.

Thus, our data show that the model accurately predicts the iris contour under the usual conditions under which the assumptions apply. The nature of the assumptions, however, must be kept in mind to understand the clinical circumstances under which the model would not apply.

ACKNOWLEDGMENT

James Tiedeman, M.D., shared his theoretical analysis and provided the computer code for iterative solution of his mathematical model when values for a, b, and z are provided. Joyce Schiffman, M.S., and Wendy Anderson, B.A., provided statistical analysis of the data. Robert W. Knighton, Ph.D., reviewed the physical properties involved in the model.

References

1. Tiedeman, J. S.: A physical analysis of the factors that determine the contour of the iris. Am. J. Ophthalmol. 111:338, 1991.

2. Richards, D. W., Russell, S. R., and Anderson, D. R.: A method for improved biometry of the anterior chamber with a Scheimpflug technique. Invest. Ophthalmol. Vis. Sci. 29:1826, 1988.

3. Jin, J. C., and Anderson, D. R.: The effect of iridotomy on iris contour. Am. J. Ophthalmol. 110:260, 1990.

4. Fleiss, J. L.: The Design and Analysis of Clinical Experiments. New York, John Wiley and Sons, 1986, pp. 233–235.

OPHTHALMIC MINIATURE

In the early morning for a short while the steel-yellow sun glittered distantly in the sky, fixing her like a serpent's eye as she sat propped up against the cushion staring out at the rectangle of impossible light.

Paul Bowles, *The Sheltering Sky*
New York, Vintage Books, 1990, pp. 295 and 296

The Influence of Iris Pigmentation on the Miotic Effect of Thymoxamine

D. L. Chris Diehl, M.D., F.R.C.S.C, Alan L. Robin, M.D., and Martin Wand, M.D.

We performed a randomly assigned, double-masked, placebo-controlled study in 78 patients with varied iris pigmentation to evaluate the influence of iris pigmentation on the ability of 0.1% thymoxamine to reverse mydriasis produced by 2.5% phenylephrine. Patients were chosen so that a 1.6:1 ratio of dark to light irides was obtained. Within one-half hour after medication, thymoxamine-treated nonbrown irides constricted significantly compared to their fellow placebo-treated irides ($P < .001$). Thymoxamine-treated pupils of nonbrown irides were 1.0 to 3.1 mm smaller than placebo-treated fellow eyes. Thymoxamine-treated light brown irides constricted less (0.6 to 2.0 mm) and more slowly compared to fellow placebo-treated irides. Thymoxamine did not reverse the mydriasis in eyes of patients with dark brown irides. Thymoxamine appears similar to other adrenergic agents that bind to melanin, delaying onset and strength of action. Its efficacy as presently formulated may be limited, in part, by iris color.

THYMOXAMINE is an alpha-1-adrenergic antagonist (sympatholytic). In the eye, it competes with adrenergic agents (including norepinephrine) at postsynaptic alpha-1-adrenoreceptors,[1] which relaxes the dilator muscle of the iris. Alternatively, thymoxamine increases miosis (reverses mydriasis) by altering the balance of parasympathetic iris sphincter tone and sympathetic iris dilator muscle tone.

Thymoxamine has many potential uses.[2] Thymoxamine (0.5%) alone has ended attacks of acute angle-closure[3] and may be useful in the diagnosis of latent angle-closure glaucoma.[4] Long-term therapy with thymoxamine in eyes with pigmentary glaucoma might reduce pigment dispersion and lessen the severity of this type of glaucoma.[5] Thymoxamine does not completely reverse the pupillary dilation associated with cycloplegic mydriatics.[6] Despite this, it might reduce the pupillary aperture sufficiently to relieve symptoms of glare and photophobia associated with a routine examination with a dilated pupil.[7]

Previous thymoxamine formulations do not alter aqueous formation,[8] outflow,[9] or intraocular pressure[9] in humans. Additionally, unlike pilocarpine, thymoxamine has no effect on the ciliary body. Hence, it does not cause ciliary spasm or narrow the anterior chamber depth.[10,11]

Thymoxamine does effectively reverse mydriasis induced by phenylephrine alone.[12-14] A dose response study found thymoxamine 0.1% is the lowest concentration that acts rapidly with minimal side effects to counter mydriasis induced by 2.5% phenylephrine.[13] Darkly pigmented irides, however, might not be as responsive to 0.1% thymoxamine as those with light pigmentation.[14] To evaluate further the effect of iris pigmentation, we studied the effect of 0.1% thymoxamine on the reversal of mydriasis induced by 2.5% phenylephrine.

Subjects and Methods

We used 0.1% thymoxamine hydrochloride or 2-(6-acetoxy-4-isopropyl-m-tolyloxy) ethyldimethylammonium hydrochloride. This formulation and the previous thymoxamine formulations (4-[2-dimethylaminoethyl] 5-iso-

Accepted for publication Dec. 13, 1990.

From the Glaucoma Service, Wilmer Eye Institute, Johns Hopkins University, and Sinai Hospital, Baltimore, Maryland (Drs. Diehl and Robin); and Department of Ophthalmology, Hartford Hospital, Hartford, Connecticut (Dr. Wand). This study was supported in part by an ARVO/CIBA-GEIGY Postdoctoral Fellowship (Dr. Diehl) and by IOLAB Pharmaceuticals.

Reprint requests to Alan L. Robin, M.D., 6115 Falls Rd., Baltimore, MD 21209-2226.

propyl-2-methyl phenyl acetate) (moxisylyte) require refrigeration and protection from light. The placebo we used was 1% polyvinyl alcohol, dextrose anhydrous, edetate disodium, benzalkonium chloride, and sterile water.

We recruited normal volunteers of either sex and any race, between the ages of 18 and 65 years. Pregnant and nursing women were excluded. All premenopausal women received a screening urine beta human chorionic gonadotropin pregnancy test before participation.

Subjects were excluded if they wore contact lenses, or if they had a past or present ocular abnormality, previous intraocular surgery, heterochromia, or known allergy to the use of phenylephrine or thymoxamine. The study was approved by the Food and Drug Administration and each institution's investigational review board. Informed consent was obtained from each subject after the nature of the study had been fully explained.

In all subjects, a prestudy medical and ophthalmic history was taken, and an ophthalmic examination was performed, including Snellen visual acuity, slit-lamp microscopy, Goldmann applanation tonometry, and ophthalmoscopy.

A camera system, designed to give 1:1 magnification, was used to photograph subjects' pupils, in color, before and after dilation and at intervals during the study. Photographs were taken with constant background illumination after instructing the subject to look into the distance, which avoided accommodation. Participants were asked to remain indoors for the duration of the study, which prevented light-induced parasympathetic stimulation of miosis from affecting the results. Horizontal pupil diameter measurements (to the nearest 0.5 mm) were made from the photographs. We used a transilluminating light source at maximum intensity for maximum contrast while measuring pupil diameter.

At the initial examination, irides were designated as either dark (including brown, dark hazel, and dark gray) or light. Patients were recruited to give a 1.6:1 ratio of dark to light irides. Thymoxamine was randomly assigned, within each iris pigmentation category, to one eye and the placebo to the fellow eye of the same subject.

Timed events began with an initial photograph and intraocular pressure measurement, followed by the instillation of two drops of 2.5% phenylephrine, five minutes apart, into both eyes of each subject. Forty minutes after the second drop of phenylephrine was instilled (pupils dilated, time 0), the pupils were again photographed. One eye then received one drop of the active drug, and the fellow eye received one drop of placebo. This occurred in a double-masked random fashion. The fellow eye acted as a control because there is no evidence of a contralateral effect with thymoxamine.

Pupils were again photographed at intervals of ½, 1, 1½, two, three, four, five, six, seven, and eight hours after instillation of the test drops. Intraocular pressure was also measured by applanation tonometry at four and eight hours after instillation of the test drops.

Subjects were asked to comment on any symptoms or adverse reactions that occurred throughout the course of the study. They were also instructed to report to the investigator any symptoms or adverse reactions that occurred after the completion of the study, which they suspected might be study-related.

Follow-up ophthalmic examinations, including pupil photographs and intraocular pressure measurement, were performed in the same manner as the initial examination one week after each subject's completion of the study.

Because the initial iris color classification included dark gray and dark hazel with brown irides in the dark grouping and because classification was subjective, occurring at two different sites, a single observer later reviewed the photographs of all 78 participants. Irides were then reassigned into five grades of iris pigmentation: light nonbrown (for example, blue, gray, hazel), medium nonbrown, light brown, medium brown, and dark brown. Subsequent analysis disclosed that only three grades of iris pigmentation showed a statistically significant different reaction to thymoxamine: nonbrown, light brown (combining our previous groups light brown and medium brown), and dark brown.

Data are presented as mean ± 1 standard deviation and were evaluated using paired *t*-tests and chi-square tests.

Results

Of the 40 subjects examined at the Sinai Hospital in Baltimore, Maryland, 27 were women and 13 were men. They ranged in age from 18 to 61 years (mean, 36 ± 11 years). Twenty-six subjects were white and 14 were black. At the initial recruitment, 25 subjects had dark irides and 15 had light irides. At the final classification, 14 subjects had dark brown irides, two had light brown irides, and 24 had nonbrown irides.

Of the 38 subjects examined at the Hartford Hospital in Hartford, Connecticut, 31 were women and seven were men. They ranged in age from 19 to 64 years (mean, 32 ± 11.1 years). Thirty-two subjects were white, three were black, and three were Hispanic. At the initial recruitment, 23 subjects had dark irides and 15 had light irides. At the final classification, six subjects had dark brown irides, 17 had light brown irides, and 15 had nonbrown irides.

There were no statistically significant differences in the pupil diameters of treated eyes compared to control eyes before dilation or when dilated at either study site or within the initial light and dark groupings. Both undilated and dilated pupil diameters, however, were significantly different comparing one study site to the other ($P < .003$). Dark and light pupils were not the same diameter before dilation (4.37 ± 1.27 mm compared with 5.10 ± 1.08 mm; $P = .01$). Dark and light dilated pupils were not significantly different in diameter (6.81 ± 1.28 mm compared with 7.27 ± 1.05 mm; $P = .09$). Because of these differences, the change in pupil diameter from the undilated to the dilated state was believed to be most meaningful and was evaluated.

Phenylephrine-induced pupil dilation was not significantly different for eyes that then received placebo compared to the dilation in eyes that then received thymoxamine (2.44 ± 1.14 mm compared with 2.34 ± 1.11 mm). Additionally, there was no significant difference in pupil diameter increase by study site or by comparing light and dark iris groups. The degree of variability of mydriasis induced by phenylephrine was also not related to iris color.

Hence, before the instillation of medication, pupils of both placebo and treated eyes had comparable diameters. The subsequent response to thymoxamine or placebo was judged as a change in pupil diameter from its dilated size at time 0 (the time of thymoxamine or placebo instillation). Note that change in pupil diameter from time 0 (thymoxamine-treated minus placebo-treated) is an indicator of thymoxamine effect.

After instillation of placebo, 60 of 78 pupils (77%) continued dilating for a short time, which increased the average pupil size for the group by 0.57 ± 0.68 mm 30 minutes later. Although 14 placebo-treated pupils (18%) constricted slightly (1 mm or less, compared to dilated pupils) by one hour after receiving the placebo drop, their mean diameters were still 2.77 ± 1.19 mm greater than their undilated diameters ($P < .001$). Pupils in placebo-treated eyes returned to their undilated average diameter between five and six hours after placebo instillation (Figs. 1 and 2).

Alternatively, most thymoxamine-treated pupils responded rapidly. Of 78 pupils, 57 (73%) constricted within the first 30 minutes. Only 21 pupils (27%) dilated further in the first 30 minutes. This group included 12 (60%) of the dark brown and eight (42%) of the light brown irides. No blue eyes continued to dilate. The mean pupil diameter returned to its undilated size 3½ hours after thymoxamine instillation (one hour for light irides, more than four hours for dark irides). Pupil diameter became smaller (0.59 ± 1.06 mm) than the undilated diameter at six hours after thymoxamine instillation ($P = .002$). Of 78 thymoxamine-treated pupils, 77 (99%) returned to or became smaller than their undilated diameter. Both light and dark placebo-treated pupils returned to within 1.0 mm of their undilated diameter at four hours.

Mean pupil diameter of thymoxamine-treated eyes in three gradations of iris pigmentation (nonbrown, light brown, and dark brown) disclosed a graduated thymoxamine effect.

The number of pupils that continued to dilate after receiving the thymoxamine were two of 39 (5%) in the nonbrown group, eight of 19 (42%) in the light brown group, and 14 of 20 (70%) in the dark brown group ($P < .05$). The number of pupils showed more than a 1.0-mm difference between thymoxamine-treated and placebo-treated eyes were 38 of 39 (97%) in the nonbrown group, 16 of 19 (84%) in the light brown group, and three of 20 (15%) in the dark brown group. The number of pupils that returned to their undilated baseline state at two hours after thymoxamine treatment were 26 of 39 (67%) in the nonbrown group, nine of 19 (47%) in the light brown group, and five of 20 (25%) in the dark brown group. The number of pupils that became more than 0.5 mm smaller than placebo-treated pupils after four hours were 26 of 39 (67%) in the nonbrown group, 12 of 19 (63%) in the light brown group, and two of 20 (10%) in the dark brown group.

Thymoxamine failed to reverse phenylephrine-induced mydriasis significantly in eyes with dark brown irides at any time during the study when comparison was performed using mean data. This group consisted entirely of black and Hispanic subjects. In this group of 20 subjects, nine did respond individually to thymoxamine instillation but with great variability in time of response.

Division of subjects with nonbrown irides

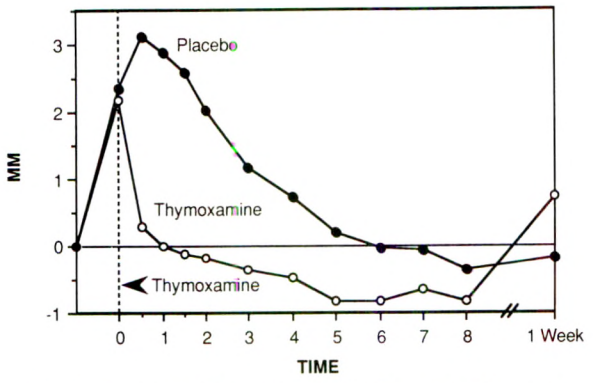


Fig. 1 (Diehl, Robin, and Wand). The mean horizontal pupil diameter change from baseline in nonbrown (light) colored irides.

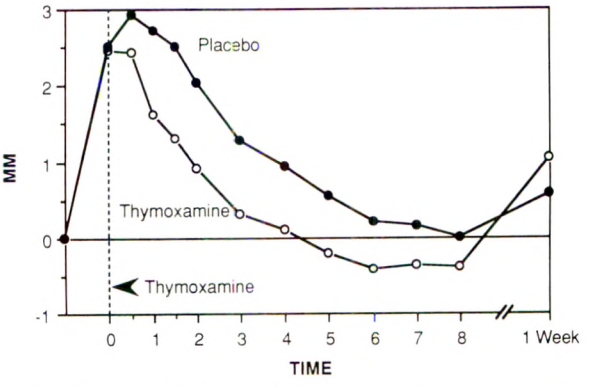


Fig. 2 (Diehl, Robin, and Wand). The mean horizontal pupil diameter change from baseline in dark irides (brown, dark gray, dark hazel).

into four groups by age showed that thymoxamine reversal of phenylephrine-induced mydriasis was age independent. Average pupil diameter for all age groups returned to the undilated diameter by one hour after thymoxamine instillation. Thymoxamine had no significant effect on the intraocular pressure of thymoxamine-treated eyes compared to placebo-treated eyes at any time during the study.

Of 78 subjects, 35 (45%) reported side effects in the thymoxamine-treated eye and 37 (47%) reported side effects in the placebo-treated eye. Side effects were mostly brief and mild and consisted of stinging, burning, and blurring of vision. One subject, who had a history of moderate to severe motion sickness, reported severe vertigo and moderate ringing in the ear for 30 seconds and a mild sense of pressure in the thymoxamine-treated eye for one hour. There were no lasting side effects.

Discussion

A drug's action is modified by its binding to different tissues and pigments.[15] Drugs with an affinity for melanin accumulate in the pigmented uveal tissues, which act as a reservoir, and are released slowly.[16,17] This can result in a slowed onset of medication effect and also a prolonged and lessened effect of the medication.

Both alpha- and beta-adrenergic agents can be affected by iris pigmentation or melanin.[16,17] The effect of various miotics and mydriatics is less intense in more darkly pigmented irides.[18] Relf and associates[14] observed that lighter colored irides responded more quickly and more completely to thymoxamine than did brown irides. We designed this study to document better the action of thymoxamine in relation to iris pigmentation. Although Relf and associates[14] found that the pupil diameter in 36 of 40 thymoxamine-treated eyes (90%) returned to baseline in one hour, we observed that the pupil diameter in 58 of 78 eyes (74%) returned to baseline (undilated state) at one hour after thymoxamine instillation. The difference in these two studies is caused by a different number of darkly pigmented irides in each study. Relf and associates[14] included four patients with dark irides that failed to respond to thymoxamine, whereas we had 20 patients with darkly pigmented irides. The pupil diameter of none of the 20 darkest brown irides returned to within 0.5 mm of baseline in less than 2½ hours, and there was no statistically significant thymoxamine effect seen in this group of patients using mean data.

Comparison of the mean difference in pupil size between thymoxamine-treated and placebo-treated eyes showed that thymoxamine was significantly better than placebo in reversing the effects of phenylephrine-induced mydriasis in both of the initial subject groupings of light and dark irides. This division of pigmentation, however, was flawed in including dark hazel and dark gray pupils with more darkly pigmented irides. Reassignment of subjects into three groups with graded iris pigmentation (nonbrown, light brown, and dark brown) disclosed that the miotic effect of thymoxamine and its speed of onset decreased with greater iris pigmentation (Fig. 3). The miotic effect and its speed of onset was greatest in eyes with nonbrown irides. The miotic effect

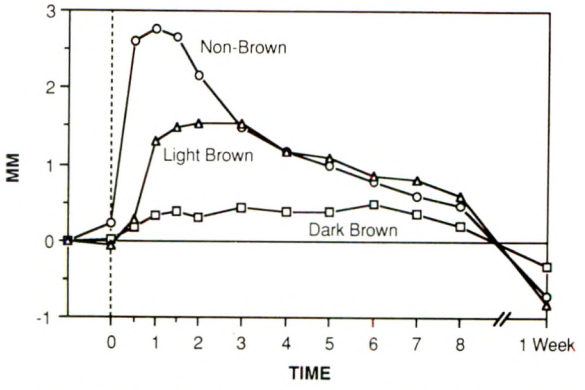


Fig. 3 (Diehl, Robin, and Wand). Pupil change from baseline in thymoxamine-treated and placebo-treated eyes for three gradations of iris pigmentation.

was reduced, and its speed of onset was delayed in eyes with light brown irides. Additionally, those irides that were most darkly pigmented (eyes of black and Hispanic subjects) did not show a statistically significant reversal of mydriasis from one drop of 0.1% thymoxamine.

Individual responses to thymoxamine seen in some of the darkly pigmented irides, however, suggest that concentrations of thymoxamine greater than 0.1% or repeated instillation of these eyedrops might be expected to overcome the pigment reservoir effect. A dose response study of the efficacy of thymoxamine reversal of phenylephrine-induced mydriasis in black subjects would be useful to determine the optimum concentration for use with their more darkly pigmented irides. Regrettably, increased side effects (stinging, burning, and the like) that occur with higher concentrations limit the usefulness of higher concentrations of thymoxamine in the darkly pigmented iris.

There was some limited overlap in the pupillary response to thymoxamine among subjects with different colored irides. We cannot prove that factors other than iris pigmentation might account for the differences we observed. These differences may relate to genetic factors or corneal permeability.

References

1. Lee, D. A., Rimele, T. J., Brubaker, R. F., Nagataki, S., and Van Houtte, P. M.: Effect of thymoxamine on the human pupil. Exp. Eye Res. 36:655, 1983.

2. Wand, M., and Grant, M. W.: Thymoxamine hydrochloride. An alpha-adrenergic blocker. Surv. Ophthalmol. 25:75, 1980.

3. Rutkowski, P. C., Fernandez, J. L., Galin, M. A., and Halasa, A. H.: Alpha-adrenergic receptor blockade in the treatment of angle-closure glaucoma. Trans. Am. Acad. Ophthalmol. Otolaryngol. 77:OP137, 1973.

4. Wand, M., and Grant, W. M.: Thymoxamine test. Differentiating angle-closure glaucoma from open-angle glaucoma with narrow angles. Arch. Ophthalmol. 96:1009, 1978.

5. Campbell, D. G.: Pigment dispersion and glaucoma. A new theory. Arch. Ophthalmol. 97:1667, 1979.

6. Shah, B., Hubbard, B., Stewart-Jones, J. H., and Edgar, D. R.: Influence of thymoxamine eye-drops on the mydriatic effect of tropicamide and phenylephrine alone and in combination. Ophthalmol. Physiol. Opt. 9:153, 1989.

7. O'Connor, P. S., Tredici, T. J., Pickett, J., Birne, B., and Peters, D. R.: Effects of routine pupillary dilation on functional daylight vision. Arch. Ophthalmol. 106:1567, 1988.

8. Lee, D. A., Brubaker, R. F., and Nagataki, S.: Effect of thymoxamine on aqueous humor formation in the normal human eye as measured by fluorophotometry. Invest. Ophthalmol. Vis. Sci. 21:805, 1981.

9. Wand, M., and Grant, W. M.: Thymoxamine HCL Effects on the facility of outflow and intraocular pressure. Invest. Ophthalmol. Vis. Sci. 15:400, 1976.

10. Susanna, R., Drance, S. M., Schulzer, M., and Douglas, G. R.: The effects of thymoxamine on anterior chamber depth in human eyes. Can. J. Ophthalmol. 13:250, 1978.

11. Saheb, N. E., Lorenzetti, D., and Saltpeter-Carlton, S.: Effect of thymoxamine and pilocarpine on the depth of the anterior chamber. Can. J. Ophthalmol. 15:170, 1980.

12. Mapstone, R.: Safe mydriasis. Br. J. Ophthalmol. 54:690, 1970.

13. DeRosia, D. R., Burns, R. R., Southwick, D. L., and Uphoff, D. L.: Determination of the minimum effective dose of thymoxamine in the reversal of phenylephrine-induced mydriasis. ARVO abstracts. Supplement to Invest. Ophthalmol. Vis. Sci. Philadelphia, J. B. Lippincott, 1988, p. 439.

14. Relf, S. J., Gharagozloo, N. Z., Skuta, G. L., Alward, W. L. M, Anderson, D. R., and Brubaker, R. F.: Thymoxamine reverses phenylephrine-induced mydriasis. Am. J. Ophthalmol. 106:251, 1988.

15. Mishima, S.: Clinical pharmacokinetics of the eye. Proctor Lecture. Invest. Ophthalmol. Vis. Sci. 21:504, 1981.

16. Patil, P. N., and Jacobowitz, D.: Unequal accumulation of adrenergic drugs by pigmented and nonpigmented iris. Am. J. Ophthalmol. 78:470, 1974.

17. Salazar, M., and Patil, P. N.: Iris pigmentation and atropine mydriasis. J. Pharmacol. Exp. Ther. 197:79, 1976.

18. Barbee, R. F., and Smith, W. O., Jr.: A comparative study of mydriatic and cycloplegic agents. Am. J. Ophthalmol. 44:617, 1957.

The Epidemiologic Association of Fuchs' Heterochromic Iridocyclitis and Ocular Toxoplasmosis

Ivan R. Schwab, M.D.

Between January 1983 and July 1987, I examined 25 patients at the Department of Ophthalmology, West Virginia University, who had the anterior segment characteristics of Fuchs' heterochromic iridocyclitis. Of these patients, 16 had fundus lesions suggestive of ocular toxoplasmosis. Of these 16 patients, 13 had a positive serologic test for toxoplasmosis, two patients were not tested, and one patient had a negative test at 1:16. The remaining nine patients with Fuchs' heterochromic iridocyclitis had no fundus lesions suggestive of toxoplasmosis. A chart review of 792 consecutive patients at the Retinal Unit, West Virginia University, during a six-month period disclosed that 24 of 590 patients (4%) had chorioretinal scars suggestive of toxoplasmosis. I concluded from these data that in at least one subgroup of patients with Fuchs' heterochromic iridocyclitis there is a significant association with the chorioretinal scars of toxoplasmosis ($P < .01$), and this is suggestive of a causal relationship.

MYSTERY AND CURIOSITY have shrouded Fuchs' heterochromic iridocyclitis since its description in 1903 by its namesake,[1] although Hutchinson[2] in 1869 or perhaps Lawrence[3] in 1843 were the first to describe the condition. We are no closer to defining the cause of this enigmatic disease than Fuchs was when he expanded his original series to include 38 cases and speculated as to cause.[4] In the interim, several theories for Fuchs' heterochromic iridocyclitis have been postulated, including an intrauterine toxin, intrauterine radiation, birth trauma, congenital abnormalities, sympathetic innervation abnormalities, tuberculosis infection, and nutritional causes.[5] None has been proven, however, and most have been discarded as possible explanations.

The classic, if not pathognomonic, physical findings of Fuchs' heterochromic iridocyclitis are often subtle and may easily escape attention even with the magnification and illumination that were not available to Fuchs.[6] Classic findings include heterochromia iridum, evanescent stellate keratic precipitates, low-grade iridocyclitis, cataract, and occasionally glaucoma, although there usually are a minimum of external signs, such as ciliary flush.

Conversely, toxoplasmosis is more easily recognized by its classic ocular manifestations in the acute and quiet stages. Certain clinical features of the active retinochoroiditis or of its chorioretinal scars are now accepted as evidence for toxoplasmosis.[7] Yet these scars may be easily missed, especially if they occur in the peripheral fundus. Additionally, we do not know if all intraocular *Toxoplasma gondii* infections manifest such scars.

Interestingly, some authors, including Fuchs, have noted chorioretinal scarring suggestive of previous inflammatory disease that may represent previous *T. gondii* infection in patients with Fuchs' heterochromic iridocyclitis.[8-12] I treated a subset of patients with Fuchs' heterochromic iridocyclitis who had chorioretinal scarring suggesting previous or active infection with *T. gondii*.

Patients and Methods

All 25 patients with the diagnosis of Fuchs' heterochromic iridocyclitis at the uveitis clinic of West Virginia University between Jan. 1, 1983, and July 30, 1987, were studied.

The diagnosis of Fuchs' heterochromic iridocyclitis, established by using the criteria of

Accepted for publication Dec. 17, 1990.

From the Department of Ophthalmology, West Virginia University, Morgantown, West Virginia.

Reprint requests to Ivan R. Schwab, M.D., Department of Ophthalmology, University of California at Davis, 1603 Alhambra Blvd., Sacramento, CA 95816.

Fuchs,[4] Franceschetti,[13] and Kimura, Hogan, and Thygeson,[10] was made on a clinical basis since no distinctive serologic or histopathologic abnormality is known to exist. The diagnostic characteristics include diffuse stromal atrophy and pigment epithelial layer atrophy of the iris, small white stellate keratic precipitates, and mild cell and flare in the anterior chamber and vitreous. All patients had heterochromia, although this was subtle in two of the brown-eyed patients, as Kimura[14] has mentioned. Usually the lighter eye was the affected eye, although the darker eye may be the affected eye if the stroma is initially light.[10,15] Iris stromal atrophy was defined as the loss of stromal substance, blunting of the iris crypts, and a dull, flat appearance to the iris surface. Iris pigment epithelium loss was defined as retroillumination defects seen with projected light reflected from the fundus.

The keratic precipitates were considered to be classic if they were seen on any visit as small to medium white deposits with fine stellate projections seen on the endothelium.[16] These keratic precipitates were never confluent or concentrated inferiorly but were distributed over most of the endothelial surface. Anterior chamber cell and flare were recorded according to the criteria of Hogan, Kimura, and Thygeson.[17]

Cataract was defined as an opacity in the crystalline lens or as aphakia. Although this definition is broad, all cataracts in this series were believed to have been capable of reducing visual acuity to at least 20/40 or worse.

Glaucoma was defined as intraocular pressure in the affected eye above 26 mm Hg on two or more visits. Patients requiring antiglaucoma medication for control of intraocular pressure were also classified as having glaucoma. Visual field defects or disk changes were not required for this diagnosis, although all four patients with chronic glaucoma did have both. Four additional patients had intermittent intraocular pressure increase without visual field or disk changes but were defined as having glaucoma.

A chorioretinal lesion was classified as consistent with toxoplasmosis if it had certain morphologic features. All such lesions were at least ½ disk diameter in size and well defined with white punched-out centers and pigmented borders. An active focus of retinochoroiditis required a yellow, cottonlike patch with an overlying vitreitis at the edge of an old chorioretinal scar attributed to toxoplasmosis. Toxoplasmosis tests, performed by reference laboratories, consisted of the indirect fluorescent antibody test to measure IgG antibody or IgG enzyme-linked immunosorbent assay.[18] Except for syphilitic serologic tests, additional testing to eliminate other causes of chorioretinal scars was not performed.

To estimate the prevalence of chorioretinal scars suggestive of toxoplasmosis in the population, I reviewed the retinal drawings of all 792 patients (344 male and 448 female) examined at the West Virginia University retinal clinic over a six-month period between Jan. 15 and July 15, 1987. Patients who had complete retinal drawings of each eye were included. Patients were excluded if any retinal drawing was incomplete. This protocol, however, accepted any patient who had only one fundus drawing or an incomplete drawing if a chorioretinal scar suggestive of toxoplasmosis existed in that drawing.

Of these 792 patients, 202 had incomplete drawings, and 82 of these had only one eye drawn completely (vitreous hemorrhage, phthisis bulbi, or no abnormality in the fellow eye). These 202 patients were excluded from calculations. Five of the remaining 590 patients were specifically referred for active or quiet toxoplasmosis. These cases could have been considered biased and hence excluded. Nevertheless, these were included as positive cases of toxoplasmosis. Ten of the 590 patients had a scar considered to be consistent with toxoplasmosis. Nine additional patients had chorioretinal scars that could have been consistent with toxoplasmosis, but these patients had other disease (for example, age-related macular degeneration or diabetes mellitus) that also could have been responsible for these scars. Chart review did not permit this determination, so these patients were classified as having chorioretinal scarring consistent with toxoplasmosis.

Results

The 25 patients with Fuchs' heterochromic iridocyclitis had some or all of the features of this classic disease (Tables 1 and 2). All patients with unilateral disease had heterochromia, with the lighter eye being the affected eye in 17 of the 25 patients. Bilateral Fuchs' heterochromic iridocyclitis does occur, and three patients had this condition in both eyes.

Of the 25 patients, 20 had fine to medium keratic precipitates scattered diffusely on the endothelium. These keratic precipitates had fine stellate projections believed to be pathog-

TABLE 1
PATIENTS WITH FUCHS' HETEROCHROMIC IRIDOCYCLITIS AND CHORIORETINAL SCARS

CASE NO., AGE (YRS), SEX	IRIS ATROPHY	CATARACT	TOXOPLASMOSIS TITER	UNUSUAL FEATURES
1, 22, F	Stromal	Posterior subcapsular	Positive*	Active toxoplasmosis lesion, developed heterochromia
2, 32, F	Stromal	Posterior subcapsular	1:512	Active toxoplasmosis lesion, vasculitis when active
3, 26, F	Stromal	Posterior subcapsular	1:64	—
4, 28, M	Stromal	Posterior subcapsular	1:64	Koeppe nodules, developed heterochromia
5, 44, F†	Stromal, pigment epithelium	Aphakic	1:16	—
6, 42, M	Stromal	Posterior subcapsular	1:64	—
7, 10, F†	Stromal, pigment epithelium	Posterior subcapsular	1:256	Toxoplasmosis scars in both eyes
8, 29, M	Stromal	No	1:64	Koeppe nodules
9, 28, F	Stromal, pigment epithelium	Posterior subcapsular	NP‡	—
10, 30, F	Stromal, pigment epithelium	Aphakic	1:512	Toxoplasmosis scars in both eyes
11, 28, F	Stromal, pigment epithelium	Aphakic	1:64	Previous vasculitis
12, 35, F†	Stromal, pigment epithelium	Aphakic	Negative	—
13, 29, M	Stromal, pigment epithelium	No	1:128	Active toxoplasmosis
14, 34, F	Stromal, pigment epithelium	No	1:16	—
15, 33, M†	Stromal, pigment epithelium	Mature	NP‡	—
16, 20, F†	Stromal	Posterior subcapsular	1:32	Toxoplasmosis scars in both eyes

*Laboratory gave no numbers.
†Approximate age.
‡NP indicates not performed.

nomonic for Fuchs' heterochromic iridocyclitis. All patients had diffuse iris stromal atrophy with loss of crypts and iris substance. Usually, this iris atrophy was associated with increased visibility of the radial iris vessels. Peripupillary iris pigment epithelium loss was noted in a patchy distribution, but only 17 of these patients had pigment epithelium loss away from the pupil. No posterior synechiae were seen.

Five of the 25 patients had previous cataract extraction and had unilateral aphakia or pseudophakia before the first examination. Eight additional patients became aphakic or pseudophakic during the study period. Nine of the remaining 12 phakic patients had posterior subcapsular or cortical cataract changes.

Ophthalmoscopy disclosed a chorioretinal scar suggestive of toxoplasmosis in 16 of 25 of these patients (Table 1). At least three of the 16 patients with Fuchs' heterochromic iridocyclitis had bilateral chorioretinal scarring. Toxoplasmosis tests were positive in 13 of these 16 patients. One of the remaining patients had a negative test, although the titers were only diluted to 1:16. The titers were not tested to undiluted serum, as has been considered necessary to rule out toxoplasmosis.[10] Two of the 16 patients did not have a blood sample drawn.

TABLE 2
PATIENTS WITH FUCHS' HETEROCHROMIC IRIDOCYCLITIS WITHOUT CHORIORETINAL SCARS

CASE NO., AGE (YRS), SEX	IRIS ATROPHY	CATARACT	TOXOPLASMOSIS TITER	UNUSUAL FEATURES
17, 29, F	Stromal, pigment epithelium	Dense	1:16	Gliotic membrane and disk
18, 22, M	Stromal, pigment epithelium	Posterior subcapsular	High positive*	—
19, 64, M	Stromal, pigment epithelium	Aphakic	1:512	—
20, 36, M	Stromal, pigment epithelium	Posterior subcapsular	1:16	Bilateral
21, 32, F	Stromal, pigment epithelium	Posterior subcapsular, cortical	1:512	—
22, 28, F	Stromal, pigment epithelium	Posterior subcapsular	<1:8	—
23, 48, M	Stromal, pigment epithelium	Dense	NP†	Bilateral, no examination of fundus
24, 32, M	Stromal	Posterior subcapsular, nuclear sclerosis	NP	—
25, 86, M	Stromal, pigment epithelium	Posterior subcapsular, nuclear sclerosis	NP	Bilateral

*Laboratory gave no numbers.
†NP indicates not performed.

Five of the patients with Fuchs' heterochromic iridocyclitis without chorioretinal scarring had positive serologic tests for *T. gondii*, and one such patient had a negative test at 1:8. The three remaining patients with Fuchs' heterochromic iridocyclitis and no chorioretinal scarring did not have tests performed.

Of 590 patients examined in the retina clinic, 24 (4%) had chorioretinal scars considered to be consistent or possibly consistent with toxoplasmosis. Of 25 patients with Fuchs' heterochromic iridocyclitis, 16 had chorioretinal scars consistent with toxoplasmosis. These two populations are significantly different ($P < .01$, chi-square, Yates correction).

Discussion

Fuchs himself noted a peripheral choroiditis in some of the patients in his 1906 article.[4] Numerous other investigators have found chorioretinal scars in patients with Fuchs' heterochromic iridocyclitis.[1,6,7,16,19-21] Initially, tuberculosis was thought to be responsible, which led to an early hypothesis linking tuberculosis and Fuchs' heterochromic iridocyclitis. Some investigators found evidence of tuberculosis in such patients.[5,22,23] We suspect, however, that in the early part of the 20th century the incidence of tuberculosis in the general population must have been greater than today. Hence, the association may have been, and probably was, coincidental.[10]

Jankü[24] documented *T. gondii*, an obligate intracellular parasite, as the organism probably responsible for certain chorioretinal scars as well as for retinochoroiditis in 1923. Later in the century, other investigators extended this work to prove that *T. gondii* was indeed responsible for active retinochoroiditis.[25,26] Hence, early investigators may not have considered *T. gondii* as a possible cause for Fuchs' heterochromic iridocyclitis. Many of these chorioretinal scars described by early investigators and ascribed to tuberculosis may well have been consistent with toxoplasmosis.

De Abreu, Belfort, and Hirata[8] suggested that these chorioretinal scars might be caused by toxoplasmosis and that a relationship might exist between these chorioretinal scars and

Fuchs' heterochromic iridocyclitis. Although these investigators found a high prevalence of chorioretinal scars in patients with Fuchs' heterochromic iridocyclitis, no attempt was made to compare this rate to the prevalence of chorioretinal scars in a similar population without Fuchs' heterochromic iridocyclitis.

The investigation by de Abreu, Belfort, and Hirata[8] is noteworthy for several reasons. Chorioretinal scars characteristic of ocular toxoplasmosis were present in 13 of 23 patients with Fuchs' heterochromic iridocyclitis. All of these patients had the distinct characteristics that allowed diagnosis of toxoplasmosis and Fuchs' heterochromic iridocyclitis, and all of these 13 patients had positive serum immunofluorescent reactions for toxoplasmosis.[8]

Although these authors were among the first to focus on *T. gondii* as the causative organism, other investigators have mentioned the possibility. Both Nemetz[27] and Kimura, Hogan, and Thygeson[10] mentioned obtaining *T. gondii* tests on their patients with Fuchs' heterochromic iridocyclitis, but neither addressed the results. Kimura, Hogan, and Thygeson[10] did mention that two of 22 patients with Fuchs' heterochromic iridocyclitis had a positive skin test for *T. gondii*, but serologic results were not reported.[10]

Some of the patients of de Abreu, Belfort, and Hirata[8] had an active posterior uveitis consistent with toxoplasmosis, as did three of the patients in our study. One of our patients with lesions resembling toxoplasmosis initially had the characteristic keratic precipitates of Fuchs' heterochromic iridocyclitis but no heterochromia. During follow-up examinations, this patient developed heterochromia unrelated to activity of the posterior segment disease. De Abreu, Belfort, and Hirata had a similar case.[8]

Other investigators in Europe have made similar observations. Saraux, LaRoche, and Le Hoang noted that ten of 13 patients with Fuchs' heterochromic iridocyclitis had chorioretinal lesions suggestive of toxoplasmosis.[28] Serum and aqueous humor IgG levels confirmed toxoplasmosis in six of these ten patients, and the other four patients were not tested. Some of the chorioretinal scars were peripheral and only seen with a three-mirror examination of the retina.[29]

In the United States, Arffa and Schlaegel[9] reported a higher prevalence of chorioretinal scars in patients with Fuchs' heterochromic iridocyclitis. De Abreu, Belfort, and Hirata[8] studied patients in Brazil where there is a high prevalence of toxoplasmosis. One could argue that the prevalence of toxoplasmosis lesions in Fuchs' heterochromic iridocyclitis in Brazil is not higher than the normal population. Arffa and Schlaegel, however, described patients primarily from Indiana. Although the prevalence of toxoplasmosis is not precisely known in this Indiana population, Arffa and Schlaegel compared the patients with Fuchs' heterochromic iridocyclitis to patients with HLA-B27–positive uveitis and found that chorioretinal scarring was significantly more common in the patients with Fuchs' heterochromic iridocyclitis.[9] Certainly, some bias may be introduced in choosing these control subjects, since this HLA-B27 group might conceivably be protected against *T. gondii* or other agents. Still, the difference in prevalence is persuasive evidence that some association exists between chorioretinal scars and Fuchs' heterochromic iridocyclitis.

Of 67 patients with Fuchs' heterochromic iridocyclitis in Arffa and Schlaegel's study, seven (10%) had lesions consistent with toxoplasmosis. These investigators were strict in the determination of scars consistent with toxoplasmosis. They excluded another 12 patients who had chorioretinal scars that could have been caused by toxoplasmosis, with at least two of these patients having positive tests for toxoplasmosis.[9] Moreover, because this was a retrospective review, we do not know if careful examination, especially of the peripheral retina, would have increased the number of patients with chorioretinal scars.

Other epidemiologic evidence is available that would suggest that the prevalence of chorioretinal scars in these patients with Fuchs' heterochromic iridocyclitis in our study, as well as those patients described by Arffa and Schlaegel, is high. Smith and Ganley[29] found that only five of 842 patients (0.6%) of the general population in a Maryland community had chorioretinal scars suggestive of previous toxoplasmosis. Similarly, Maetz and associates[30] described a prevalence rate of chorioretinal scars resembling toxoplasmosis in patients from Alabama that ranged from a low of six per 1,000 to a high of 88 per 1,000.[30]

Similarly, in my chart review of 792 patients with retinal abnormalities who had retinal drawings, I found a prevalence of no more than 24 of 590 (4%) having scars typical of toxoplasmosis. This may greatly overestimate the prevalence of such scars in this population since I included any such scar based only on the retinal drawings. Although this patient group may have a Berksonian bias,[31] these patients do rep-

resent a referral group drawn from the same patient population as the ones with Fuchs' heterochromic iridocyclitis. Still, it is important to realize that these patients with retinal abnormalities are not a random sample. All had retinal disorders, predominantly vascular and degenerative, and the selection of this group may have some inherent bias.

The findings of Fuchs' heterochromic iridocyclitis can be subtle and evanescent. The scars of toxoplasmosis may be peripheral and may be missed without careful retinal examination. Cataract, commonly found in patients with Fuchs' heterochromic iridocyclitis, may obscure observation of the peripheral retina. Alternatively, *T. gondii* may infect the eye in an unsuspected site other than the retina, such as the ciliary body, vitreous, or glial cell. The findings in five patients with Fuchs' heterochromic iridocyclitis and positive *T. gondii* tests but no chorioretinal scars suggest this alterative site theory. Without an understanding of the prevalence of seropositivity in this population, however, these data may not be particularly useful. Perkins[21] reported that positive *T. gondii* tests were present in 792 of 1,065 patients (70%) with chronic anterior uveitis. Moreover, in some populations, nearly universal seropositivity to *T. gondii* was found to occur by adulthood.[32]

Although other authors have described patients with Fuchs' heterochromic iridocyclitis and the chorioretinal scars of toxoplasmosis, this study provides epidemiologic evidence of an association between the posterior segment findings consistent with toxoplasmosis and the anterior segment findings of Fuchs' heterochromic iridocyclitis. Alternatively, patients with ocular toxoplasmosis may coincidentally have physical findings that closely resemble Fuchs' heterochromic iridocyclitis. The amount of anterior segment inflammation may be sufficient to cause the subtle changes such as heterochromia, posterior subcapsular cataract, and low-grade inflammation. Indeed, five of the 16 patents with Fuchs' heterochromic iridocyclitis and chorioretinal scars did not have the typical keratic precipitates of Fuchs' heterochromic iridocyclitis. Perhaps ocular toxoplasmosis can create a chronic condition that can resemble Fuchs' heterochromic iridocyclitis but not have the same pathogenesis. Nevertheless, future investigations should consider Fuchs' heterochromic iridocyclitis to be related to or caused by an infectious agent such as *T. gondii*.

References

1. Fuchs, E.: Lehrbuch der Augenheilkunde, ed. 9. Leipzig, Germany, F. Deuticke, 1903, pp. 494. Cited in Loewenfeld, I. E., and Thompson, H. S.: Fuchs' heterochromic cyclitis. A critical review of the literature. I. Clinical characteristics of the syndrome. Surv. Ophthalmol. 17:394, 1973.
2. Hutchinson, J.: Unsymmetrical ocular peculiarities in patient whose irides were of different colours. R. Lond. Ophthalmol. Hosp. Rep. 6:44, 1869. Cited in Loewenfeld, I. E., and Thompson, H. S.: Fuchs' heterochromic cyclitis. A critical review of the literature. I. Clinical characteristics of the syndrome. Surv. Ophthalmol. 17:394, 1973.
3. Lawrence, W.: Changes in colour in iris. In Hays, I. (ed.): A Treatise of Diseases of the Eye. Philadelphia, Lea and Blanchard, 1843, pp. 411–416.
4. Fuchs, E.: Ueber komplikationen der heterochromie. Z. Augenheilkd. 159:191, 1906.
5. Loewenfeld, I. E., and Thompson, H. S.: Fuchs' heterochromic cyclitis. A critical review of the literature. II. Etiology and mechanisms. Surv. Ophthalmol. 18:2, 1973.
6. Hollwich, F.: Zur differential diagnose der heterchromiezyklitis. Klin. Monatsbl. Augenheilkd. 142:129, 1963.
7. O'Connor, G. R.: Manifestations and management of ocular toxoplasmosis. Bull. N. Y. Acad. Med. 50:192, 1974.
8. de Abreu, M. T., Belfort, R., Jr., and Hirata, P. S.: Fuchs' heterochromic cyclitis and ocular toxoplasmosis. Am. J. Ophthalmol. 93:739, 1982.
9. Arffa, R. C., and Schlaegel, T. F.: Chorioretinal scars in Fuchs' heterochromic iridocyclitis. Arch. Ophthalmol. 102:1153, 1984.
10. Kimura, S. J., Hogan, M. J., and Thygeson, P.: Fuchs' syndrome of heterochromic cyclitis. Arch. Ophthalmol. 54:179, 1955.
11. Saraux, H., LaRoche, L., and Le Hoang, P.: Secondary Fuchs' heterochromic cyclitis. A new approach to an old disease. Ophthalmologica 190:193, 1985.
12. O'Connor, G. R.: Heterochromic iridocyclitis. Trans. Ophthalmol. Soc. U. K. 104:219, 1985.
13. Franceschetti, A.: Heterochromic cyclitis (Fuchs' syndrome). Am. J. Ophthalmol. 39:50, 1955.
14. Kimura, S. J.: Fuchs' syndrome of heterochromic cyclitis in brown-eyed patients. Trans. Am. Ophthalmol. Soc. 76:76, 1978.
15. Sugar, H. S.: Heterochromia iridis. Am. J. Ophthalmol. 60:1, 1965.
16. Liesegang, T.: Clinical features and prognosis in Fuchs' uveitis syndrome. Arch. Ophthalmol. 100:1622, 1982.
17. Hogan, M. J., Kimura, S. J., and Thygeson, P.: Signs and symptoms of uveitis. I. Anterior uveitis. Am. J. Ophthalmol. 47:155, 1959.
18. McCabe, R. E., and Remington, J. S.: The diag-

nosis and treatment of toxoplasmosis. Eur. J. Clin. Microbiol. 2:95, 1983.

19. Calixto, N.: Ciclite heterochromica de Fuchs glaucoma. Rev. Bras. Oftamol. 37:331, 1978. Cited in de Abreu, M. T., Belfort, R., Jr., and Hirata, P. S.: Fuchs' heterochromic cyclitis and ocular toxoplasmosis. Am. J. Ophthalmol. 93:739, 1982.

20. François, J., and Mastilovic, B.: L'heterochromie de Fuchs associee aux heredodegenerescences chorioretinennes. Ann. Ocul. 19:385, 1961.

21. Perkins, E. S.: Heterochromic Cyclitis (Fuchs' Syndrome) in Uveitis and Toxoplasmosis. Boston, Little, Brown and Company, 1961, pp. 42–49.

22. King, C.: Tuberculous iridocyclitis as a cause of the heterochromia of Fuchs. Trans. Am. Ophthalmol. Soc. 25:380, 1927.

23. Lloyd, R. I.: Heterochromia and allied conditions with case reports. Am. J. Ophthalmol. 14:287, 1931.

24. Jankü, J.: Pathogenesa a pathologická Anatomic Tak nazvaného vrozeného kolobomu ž Ïute Skvrny v oku Normálnë velikem a mikrophthalmickem s nalesem Parasitü v sítnici. Cas. Lek. Ces. 67:1021, 1923. Cited in O'Connor, G. R.: Manifestations and management of ocular toxoplasmosis. Bull. N. Y. Acad. Med. 50:192, 1974.

25. Wolf, A., Cowen, D., and Paige, B. H.: Toxoplasmosis. Occurrence in infants as an encephalomyelitis. Verification by transmission to animals. Science 89:226, 1939.

26. Hogan, M. J., Zweigart, P. A., and Lewis, A.: Recovery of *Toxoplasma* from a human eye. Arch. Ophthalmol. 60:548, 1958.

27. Nemetz, V. R.: Fuchssche Heterochromie mit choroiditis dissem. bieder Augen. Wien. Klin. Wochenschr. 63:561, 1950. Cited in Loewenfeld, I. E., and Thompson, H. S.: Fuchs' heterochromic cyclitis. A critical review of the literature. I. Clinical characteristics of the syndrome. Surv. Ophthalmol. 17:394, 1973.

28. Saraux, H., LaRoche, L., and Le Hoang, P.: Syndrome de Fuchs' et cicatrice de chorioretinute toxoplasmique. Discussion pathogenique. Bull. Soc. Ophtalmol. Fr. 85:959, 1985.

29. Smith, R. E., and Ganley, J. P.: Ophthalmologic survey of a community. I. Abnormalities of the ocular fundus. Am. J. Ophthalmol. 74:1126, 1972.

30. Maetz, H. M., Kleinstein, R. N., Federico, D., and Wayne, J.: Estimated prevalence of ocular toxoplasmosis and toxocariasis in Alabama. J. Infect. Dis. 156:414, 1987.

31. Berkson, J.: Limitations of the application of four-fold table analysis to hospital data. Biometrics 2:47, 1946.

32. Adams, W. H., Kindermann, W. R., Walls, K. W., and Heotis, P. M.: *Toxoplasma* antibodies and retinochoroiditis in the Marshall Islands and their association with exposure to radioactive fallout. Am. J. Trop. Med. Hyg. 36:315, 1987.

Histopathologic Evidence of Fibrovascular Ingrowth Four Weeks After Placement of the Hydroxyapatite Orbital Implant

Carol L. Shields, M.D., Jerry A. Shields, M.D., Ralph C. Eagle, Jr., M.D., and Patrick De Potter, M.D.

We studied the histopathologic findings after placement of an orbital hydroxyapatite implant in a patient. The implant was placed after enucleation for a choroidal melanoma and was removed four weeks later because histopathologic examination of the enucleated globe disclosed tumor invasion of the optic nerve that necessitated further orbital tissue removal. Our histopathologic findings confirm that there is significant ingrowth of fibrovascular tissue in these implants, even within weeks of implantation.

THE POROUS, coral-derived hydroxyapatite sphere is gaining popularity as an implant for anophthalmic orbits and is being used instead of the standard polymethylmethacrylate sphere.[1] Clinical and histopathologic studies on the use of hydroxyapatite as a bone substitute in oral, maxillofacial, and orthopedic surgery have been encouraging.[2-7] Initial unpublished clinical studies using this material in orbital implant surgery have shown that increased motility of the ocular prosthesis can be attained (A. Perry, M.D., oral communication, September 1989). This was achieved by reattaching all six extraocular muscles to a hydroxyapatite sphere encased in sclera. Later, the prosthesis was connected to the vascularized hydroxyapatite implant through a surgically placed polymethylmethacrylate peg, which transferred the increased mobility of the implant to the prosthesis. The hydroxyapatite implant is infiltrated by fibrovascular tissue and thus becomes integrated into the orbital tissues, which prevents the complications of extrusion and infection that have occurred frequently with previous orbital integrated implants.[8] The main benefit of the hydroxyapatite sphere implant is improved appearance. The artificial eye is more natural in appearance because of increased mobility. We studied the histopathologic characteristics of a hydroxyapatite implant four weeks after implantation and found the presence and distribution of the orbital fibrovascular tissue within the pores of the hydroxyapatite sphere.

Case Report

A 69-year-old white man who had visual loss in the right eye was found to have a choroidal melanoma on clinical examination, but he declined all treatment. Two months later, he returned with severe pain in the involved eye. The choroidal melanoma had grown and had produced neovascular glaucoma. The patient was referred to the Ocular Oncology Service at our institution for examination and treatment.

On our examination, visual acuity was R.E.: counting fingers and L.E.: 20/20. Intraocular pressure was R.E.: 43 mm Hg and L.E.: 14 mm Hg. The left eye was normal. Examination of the right anterior segment disclosed diffuse iris neovascularization. Ophthalmoscopy showed an abruptly elevated, mushroom-shaped choroidal melanoma and a total retinal detachment. A-scan and B-scan ultrasonography demonstrated an echogenic mushroom-shaped choroidal mass measuring 12 mm in thickness originating from the juxtapapillary choroid. There was no evidence of extraocular extension, and the optic nerve shadow appeared

Accepted for publication Nov. 2, 1990.

From the Oncology Service (Drs. C. Shields, J. Shields, and De Potter) and Department of Pathology (Dr. Eagle), Wills Eye Hospital, Thomas Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania. This study was supported in part by the Ocular Oncology Fund and the Oncology Research Fund, Wills Eye Hospital, the Eye Tumor Research Foundation Incorporated, Gladwyne, Pennsylvania, and the Macula Foundation, New York, New York.

Reprint requests to Carol L. Shields, M.D., Oncology Service, Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

normal in caliber. Preoperative systemic examination of the patient showed normal results and included a complete physical examination, chest x-ray, complete blood cell count, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, and lactate dehydrogenase.

The eye was removed by a minimal manipulation enucleation. A 20-mm, scleral-wrapped, porous hydroxyapatite orbital implant was inserted (Fig. 1, top left). All six extraocular muscles were reattached to their normal anatomic positions on the implant (Fig. 1, top right, bottom left, bottom right). Postoperatively, the patient healed well. Histopathologic examination of the enucleated eye disclosed a mixed-cell choroidal melanoma that had invaded the parenchyma and subarachnoid space of the anterior portion of the optic nerve. Although the tumor was not present in the transverse section of optic nerve at the surgical margin, the degree of subarachnoid invasion suggested intraorbital meningeal spreading. Postoperatively, computed tomographic scans of the orbit showed the calcified hydroxyapatite implant in good position, and the optic nerve appeared normal (Fig. 2). The findings were discussed with the patient, and it was decided to remove the remaining intraorbital optic nerve as well as the perineural orbital tissue. The patient declined an orbital exenteration or external beam radiotherapy, which were the other therapeutic options.

Four weeks after implantation, the hydroxyapatite sphere was removed along with a 22-mm segment of residual optic nerve that extended to the orbital apex. Intraoperatively, all six extraocular muscles were found to be tightly adherent by their insertions to the scleral-coated implant. They were hooked and detached as normal muscles would be handled. The hydroxyapatite implant was delivered from the orbit without difficulty. The remainder of the optic nerve to the orbital apex was removed.

Histopathologic examination of the residual optic nerve disclosed multiple aggregates of

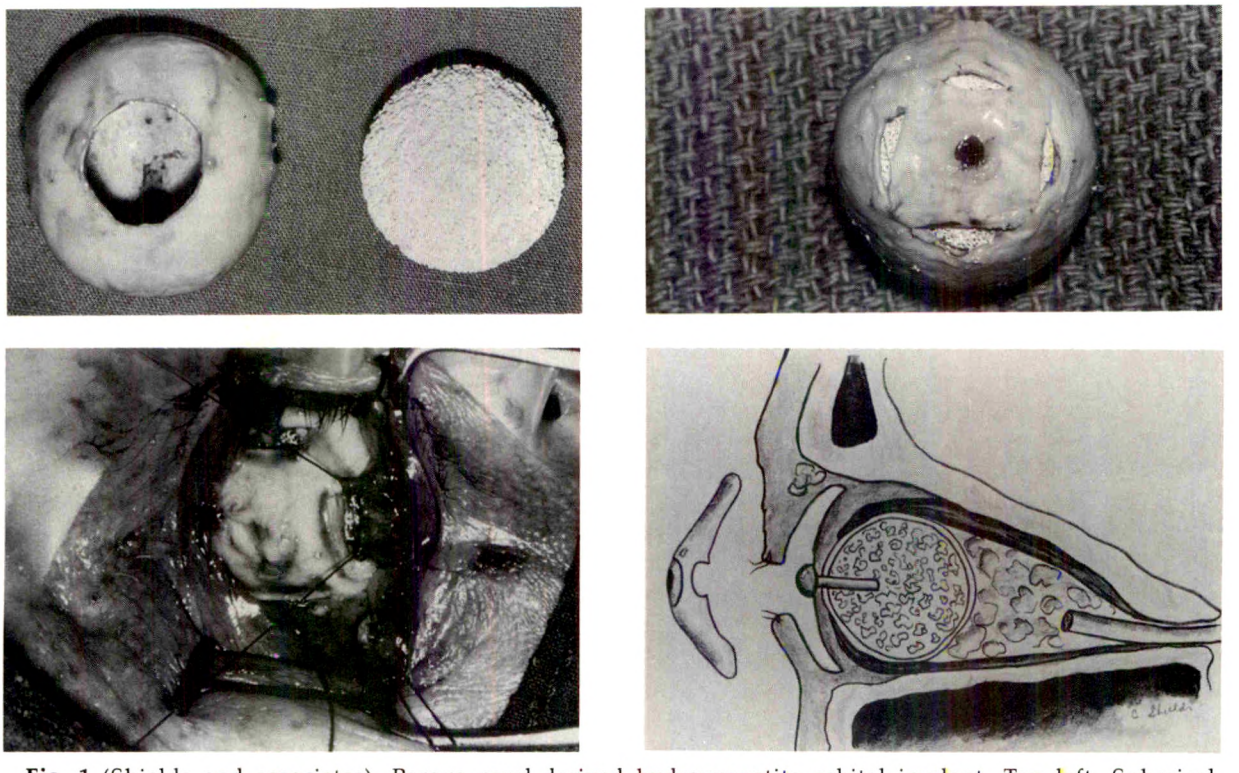


Fig. 1 (Shields and associates). Porous coral-derived hydroxyapatite orbital implant. Top left, Spherical implant and empty scleral shell that will cover the implant. Top right, Scleral-coated implant with windows cut for ingrowth of fibrovascular tissue. Bottom left, The implant is placed into the anophthalmic orbit and all extraocular muscles are reattached to their normal anatomic position. The lateral rectus muscle is being pulled toward its scleral window for attachment. Bottom right, Diagram illustrating the implanted hydroxyapatite sphere.

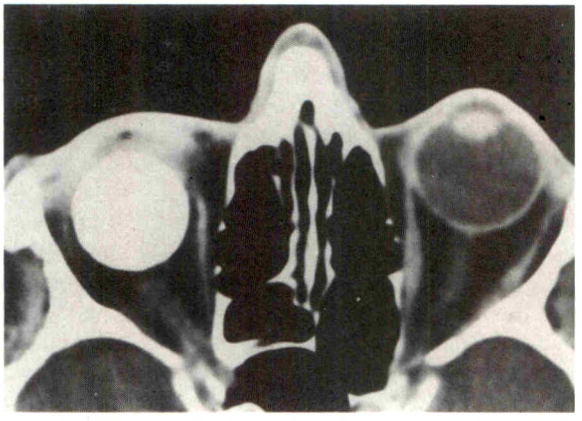


Fig. 2 (Shields and associates). Computed tomographic scan (axial section) demonstrating the heavily calcified hydroxyapatite implant and the recti muscles attached to the implant. Note the remaining optic nerve in the posterior orbit.

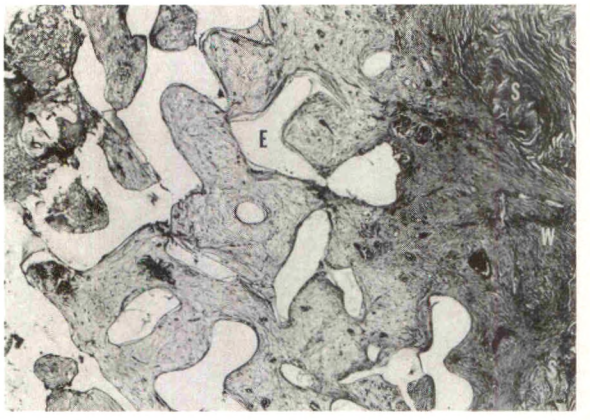


Fig. 3 (Shields and associates). Approximately four weeks after implantation, ingrowth of fibrovascular tissue emanating from a window (W) in the scleral shell (S) invaded pores in the periphery of the coralline hydroxyapatite sphere. An interconnected network of empty channels (E) was occupied by hydroxyapatite before decalcification (Masson's trichrome, × 25).

malignant melanoma cells in the pia mater and arachnoid. Immunoreactivity for melanoma-specific antigen (HMB-45) confirmed that the cellular aggregates were composed of melanoma cells. The porous surface of the hydroxyapatite ball implant was visible through several windows in the covering of sclera ensheathing the implant. Hemorrhagic fibrovascular tissue adhered to the outer surface of the scleral shell. Decalcification was necessary to allow microscopic sectioning of the hydroxyapatite implant.

Microscopic examination of the implant disclosed a discontinuous shell of sclera that was partially covered by fibroadipose orbital tissue. In the interior of the shell, most of the prosthetic material had been dissolved by the decalcifying fluid, which produced an interconnected network of empty channels. Only a small amount of residual birefringent calcific material was noted focally. Eosinophilic granular serous or serosanguineous fluid filled the pores in the implant. Peripherally the serosanguineous fluid was invaded and replaced by an ingrowth of delicate fibrovascular tissue that appeared to emanate from the windows in the scleral shell (Figs. 3 and 4). Fibrovascular ingrowth was most extensive near the scleral defects, where fibrosis extended approximately 3 mm centrally. A thin, irregular, focally basophilic condensation was present on the surface of the material filling the pores. This was thought possibly to represent residual calcium or more likely early dystrophic calcification. The hydroxyapatite prosthetic material had elicited a relatively sparse inflammatory reaction consisting of rare foreign body giant cells. The inflammation was confined to the immediate vicinity of a large scleral window. Nearby, additional foreign body giant cells surrounded particulates of foreign material and multistranded suture material.

Discussion

Hydroxyapatite implants are made from specific marine corals that have an interconnected porous structure. Closed passages or cul-de-sacs that could sequester organisms and predispose to infection are absent in this material. The porous material acts as a scaffold for the rapid ingrowth of vascularized connective tissue and bone.[3,5,9] Vascular ingrowth occurs along the walls of the pores in a creeping centripetal fashion from the periphery to the center of the implant. The use of hydroxyapatite in bone replacement has been studied. Such implants have been placed in direct contact with bone and have shown excellent biomechanical function.[2-7,9] Animal studies of hydroxyapatite implants placed in soft tissue and not in contact with bone showed evidence of soft tissue ingrowth into the material.[10]

Although dry implants are brittle, hydroxyapatite gains strength as its pores are infiltrated by connective tissue and bone. Animal studies have shown that fibrovascular ingrowth oc-

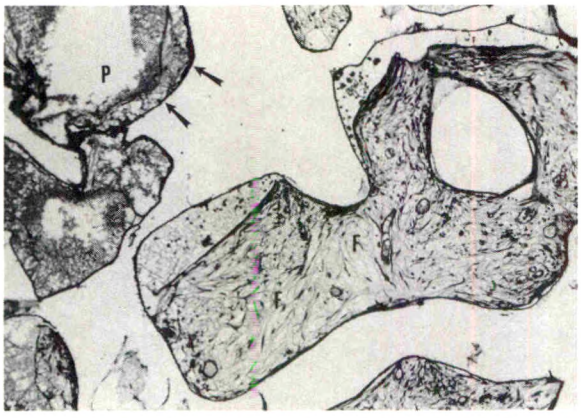


Fig. 4 (Shields and associates). Fibroblasts, capillaries, and areolar matrix of collagen fibrils constitute fibrovascular tissue (F) invading peripheral pores in the hydroxyapatite sphere. Granular inspissated proteinaceous fluid (P) fills more centrally located pores at left. Arrows mark a linear rim of calcification (Masson's trichrome, ×50).

curred as early as two weeks after placement[9] and bone ingrowth at six weeks.[11] Host bone ingrowth in humans has been demonstrated in periodontal defects and in long bone defects.[5] Kenney and associates[5] studied tissue samples from three patients who had periodontal defects treated with porous hydroxyapatite. Using light and scanning electron microscopy, they showed that connective tissue had infiltrated through the pores and a narrow zone of bone formation was present along the walls of the pores three months after implantation. Four months and six months after implantation, continued bone formation was evident with lamellar bone being prominent.

The orbital implantation differs from the maxillofacial and orthopedic implantation in that the material is not in direct contact with bone. Our findings confirm the theory that the material becomes vascularized when it is placed in soft tissue, such as in the human orbit. At four weeks, a significant amount of fibrovascular ingrowth was demonstrated in our patient, most notably at the sites of the scleral windows. A narrow rim of calcification thought possibly to represent early bone deposition also was found. Hydroxyapatite is well tolerated by the human orbit. Only rare foreign body giant cells were seen in contact with the implant material.

The primary reason for the use of hydroxyapatite in the orbit is the material's ability to become an integrated part of the orbital tissues, which makes it less likely to extrude when a peg of foreign material is placed in a hole drilled in its center. We have now used more than 50 hydroxyapatite implants after enucleation for melanoma and retinoblastoma. None of these have developed infection or extrusion of the implant. We have demonstrated that fibrovascular invasion occurs at an early stage after implantation. Vascular ingrowth could probably be encouraged even more rapidly with the use of more scleral windows or larger scleral windows as the vessels have been documented in our study to enter the hydroxyapatite through these apertures.

References

1. Shields, J. A.: Diagnosis and Management of Intraocular Tumors. St. Louis, C. V. Mosby, 1982, pp. 40–61.

2. Sartoris, D. J., Gershuni, D. H., Akeson, W. H., Holmes, R. E., and Resnick, D.: Coralline hydroxyapatite bone graft substitutes. Preliminary report of radiographic evaluation. Radiology 159:133, 1986.

3. Piecuch, J. F., Topazian, R. G., Skoly, S., and Wolfe, S.: Experimental ridge augmentation with porous hydroxyapatite implants. J. Dent. Res. 62:148, 1983.

4. White, E., and Shors, E. C.: Biomaterial aspects of Interpore-200 porous hydroxyapatite. Dent. Clin. North Am. 30:49, 1986.

5. Kenney, E. B., Lekovic, V., Sa Ferreira, J. C., Han, T., Dimitrijevic, B., and Carranza, F. A.: Bone formation within porous hydroxyapatite implants in human periodontal defects. J. Periodontol. 57:76, 1986.

6. Rosen, H. M.: Surgical correction for the vertically deficient chin. Plast. Reconstr. Surg. 82:247, 1988.

7. ———: Porous block hydroxyapatite as an interpositional bone graft substitute in orthognathic surgery. Plast. Reconstr. Surg. 83:985, 1989.

8. Spaeth, E. B.: Principles and Practices of Ophthalmic Surgery. Philadelphia, Lea & Febiger, 1948, pp. 137–165.

9. Holmes, R. E.: Bone regeneration within a coralline hydroxyapatite implant. Plast. Reconstr. Surg. 63:626, 1979.

10. Piecuch, J. F.: Extraskeletal implantation of porous hydroxyapatite ceramic. J. Dent. Res. 61:1458, 1982.

11. Finn, R. A., Bell, W. H., and Brammer, J. S.: Interpositional grafting with autogenous bone and coralline hydroxyapatite. J. Maxillofac. Surg. 8:217, 1980.

AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

EDITORIAL BOARD

Thomas M. Aaberg, *Atlanta*
Jules Baum, *Boston*
William M. Bourne, *Rochester*
Ronald M. Burde, *New York*
Fred Ederer, *Bethesda*
Frederick T. Fraunfelder, *Portland*
Michael A. Kass, *St. Louis*
Steven G. Kramer, *San Francisco*
Irving H. Leopold, *Irvine*
Robert Machemer, *Durham*
Nancy M. Newman, *San Francisco*
Don H. Nicholson, *Miami*
Edward W. D. Norton, *Miami*
Deborah Pavan-Langston, *Boston*
Allen M. Putterman, *Chicago*
Dennis Robertson, *Rochester*
Merlyn M. Rodrigues, *Baltimore*
Stephen J. Ryan, *Los Angeles*
Jerry A. Shields, *Philadelphia*
M. Bruce Shields, *Durham*
Ronald E. Smith, *Los Angeles*
Bruce E. Spivey, *San Francisco*
Bradley R. Straatsma, *Los Angeles*
H. Stanley Thompson, *Iowa City*
E. Michael Van Buskirk, *Portland*
Gunter K. von Noorden, *Houston*

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

Directors

Edward W. D. Norton, *President*
Bradley R. Straatsma, *Vice President*
Frank W. Newell, *Secretary and Treasurer*
Bruce E. Spivey
Thomas M. Aaberg
Michael A. Kass

EDITORIAL

In Defense of Animal Research

Gunter K. von Noorden

Animal rights groups in the United States and Great Britain have threatened repeatedly the continuation of vision research. The activities of these groups have ranged from intimidation and death threats directed at individual scientists to the infliction of physical damage to property, amounting to millions of dollars. Irreplaceable research data have been destroyed and experimental animals have been "liberated." The growing trend of violence in extreme animal rights organizations has recently escalated with the bombing of two cars of university veterinarians at Bristol University in England, during which a baby was injured severely. The goal of most animal rights groups is the cessation of all biomedical research that uses animals. Powerful lobbying efforts are underway in the United States and other countries to influence legislators to this effect.

These activities should not be confused with those of other organizations who are not opposed to animal research but are concerned with welfare and humane treatment of laboratory animals. Strict government and local university policies regarding animal welfare are now in effect. The abuse of experimental animals in biomedical research has become a thing of the past, since adherence to these policies is mandatory for all recipients of research grants from the National Institutes of Health.

Ophthalmologists should be aware that corneal transplantation, antiviral drugs, or the excimer laser are but a few examples of advances that would not have come about without animal research. What may be less well known are the contributions to the knowledge of normal and abnormal visual development from experiments in cats and monkeys. Much of this work has been published in basic science journals to which most clinicians have only limited access. Since it is this research that has most recently come under attack at the universities of California (Berkeley), North Carolina (Greensboro), Oregon, and Oxford, it is appropriate to recall how our current thinking and understanding about amblyopia have benefitted from this work. Because of its clinical relevance, I have selected amblyopia from the vast pool

of animal research data that are beginning to unveil how the visual system develops and functions under normal and abnormal circumstances.

Experiments in amblyopic cats and monkeys have identified structural defects in the geniculate-striate pathways and neurophysiologic functional defects of single cells in the visual cortex. In studying the different characteristics of these disturbances in the brains of monkeys with strabismic, anisometropic, and form vision deprivation amblyopia, it has become possible to identify visual deprivation and abnormal binocular interaction as the two factors that act individually or in unison to produce the clinically different forms of amblyopia.[1] We are beginning to understand the mechanism of amblyopia on a cellular level!

Despite the enormous accumulation of important psychophysical, behavioral, and electrophysiologic research data from human amblyopia research, this information could not have been obtained without animal experiments. The reason is simple: invasive extracellular recordings from the striate cortex, for obvious reasons, cannot be performed in humans. Moreover, the brain from a human with amblyopia had never become available for histologic analysis, and if it had we would not have known where in the brain to look for anomalies. Armed with the knowledge from animal experiments, however, we have been able to return to the clinical laboratory and describe histologic changes similar to those described in animals[2] in the brain from a human with amblyopia. Positron emission tomography scans have shown metabolic disturbances in parts of the striate cortex of humans with amblyopia that were known from animal experiments to be affected.[3]

The validity of the animal model has now been firmly established and the nature of some, though not necessarily all, events in the amblyopic afferent visual pathways have been identified. We can now turn our attention to finding new methods for the reversal of amblyopia. Although patching still remains the mainstay of effective treatment in young children, amblyopia in adults remains untreatable. Conversely, the potential for recovery must exist, as we have learned from clinical observations in some patients with amblyopia whose vision improved dramatically after loss of the good eye.[4] The neurochemistry of visual inhibition and its reversal as it exists in suppression and amblyopia has emerged as a promising field for future vision research for which the use of animal models will be indispensable.

Much of this research is only at its beginning and, as the critics of animal experiments are readily pointing out, may at this time be of theoretical value only. However, one cannot predict which subject of theoretical interest today may tomorrow become the cornerstone of an important clinical breakthrough.

Has the practical management and prevention of amblyopia improved as a result of animal research? Twenty-five years ago, congenital cataracts were operated on infrequently before the age of 2 or 3 years. After the operation, the eye was then left uncorrected until the child became old enough to tolerate spectacles or contact lenses. The amblyopiogenic effect of the uncorrected aphakic anisometropia was not at all appreciated by clinicians. As one may expect, the visual results after late surgery and uncorrected anisometropia were abysmal.

Increased awareness of the extraordinary sensitivity of the immature visual system and the discovery of sensitive periods from animal experiments have revolutionized our clinical management of congenital and traumatic cataracts, or other conditions that interfere with normal visual development. Cataracts are now removed routinely in early infancy, followed by immediate aphakic correction and, in unilateral instances, by rigorous amblyopia therapy. Similar guidelines have become accepted for the management of other obstacles to normal binocular visual stimulation in infants, such as corneal opacities, hyphemas, vitreous hemorrhages, and complete blepharoptosis.

In appreciating the importance of animal research, we must also remember the discovery of the unexpected during an experiment originally designed for a different purpose. Eyelid suture in kittens and infant monkeys deregulates the axial growth of the eye and causes large refractive errors, which owes its discovery to serendipity.[5] Clinical studies in human patients have confirmed this phenomenon, which has added an entirely new and fascinating dimension to the origin of human refractive errors.[6]

Why this editorial? In view of the activities of animal rights groups, the public must come to a better understanding and appreciation of the benefits derived from animal research. We, as physicians, should not underestimate our potential in public education. Most patients actually do listen to us. After successful treatment of amblyopia or visual rehabilitation after cataract surgery in childhood, the comment: "We

were able to help your child because of research that is now being threatened by animal rights groups," can be most effective in this endeavor. The time to get involved is now!

Reprint requests to Gunter K. von Noorden, M.D., Department of Ophthalmology, Texas Children's Hospital, P.O. Box 20269, 6621 Fannin, Houston, TX 77225.

References

1. von Noorden, G. K.: Amblyopia. A multidisciplinary approach (Proctor Lecture). Invest. Ophthalmol. Vis. Sci. 26:52, 1985.

2. von Noorden, G. K., Crawford, M. L. J., and Levacy, R. A.: The lateral geniculate nucleus in human anisometropic amblyopia. Invest. Ophthalmol. Vis. Sci. 24:788, 1983.

3. Demer, J. L., von Noorden, G. K., Volkow, N. D., and Gould, K. L.: Imaging of cerebral blood flow and metabolism in amblyopia by positron emission tomography. Am. J. Ophthalmol. 105:337, 1988.

4. Vereecken, E. P., and Brabant, P.: Prognosis for vision in amblyopia after loss of the good eye. Arch. Ophthalmol. 102:220, 1984.

5. Wiesel, T. N., and Raviola, E.: Myopia and enlargement after neonatal lid fusion in monkeys. Nature 266:66, 1977.

6. von Noorden, G. K., and Lewis, R. A.: Ocular axial length in unilateral congenital cataracts and blepharoptosis. Invest. Ophthalmol. Vis. Sci. 28:750, 1987.

Declaration on Animals in Medical Research

In view of the threat to medical research posed by increasingly vocal and violent campaigns for the abolition of animal experimentation, we make the following declaration.

Experiments on animals have made an important contribution to advances in medicine and surgery, which have brought major improvements in the health of human beings and animals.

Continued research involving animals is essential for the conquest of many unsolved medical problems such as cancer, AIDS, other infectious diseases, and genetic, developmental, neurological, and psychiatric conditions.

Much basic research on physiological, pathological, and therapeutic processes still requires animal experimentation. Such research has provided and continues to provide the essential foundation for improvements in medical and veterinary knowledge, education, and practice.

The scientific and medical community has a duty to explain the aims and methods of its research, and to disseminate information about the benefits derived from animal experimentation.

The comprehensive legislation governing the use of animals in scientific procedures must be strictly adhered to. Those involved must respect animal life, using animals only when essential and as humanely as possible, and they should adopt alternative methods as soon as they are proved to be reliable.

Freedom of opinion and discussion on this subject must be safeguarded, but violent attacks on people and property, hostile campaigns against individual scientists, and the use of distorted, inaccurate, or misleading evidence should be publicly condemned.

British Association for the Advancement of Science

Reprinted with permission. Br. Med. J. 301:460, 1990.

LETTERS TO THE JOURNAL

Aberrant Extraocular Fibrous Band as a Cause of Strabismus

Abraham Spierer, M.D., Howard Desatnik, M.D., and Yomtov Robert Barishak, M.D.

Goldschleger Eye Institute, Chaim Sheba Medical Center, and Sackler School of Medicine, Tel Aviv University.

Inquiries to Abraham Spierer, M.D., Goldschleger Eye Institute, Sheba Medical Center, Tel-Hashomer 52621, Israel.

Congenital anomalies of the extraocular muscles and tendons, including absence, hypoplasia, fusion, bifurcation, reduplication, or abnormal insertion of the extraocular muscles, fascial anomalies, and fibrous bands,[1] cause strabismus of peripheral origin. Such anomalies may result in incomitant strabismus, which resembles a neurogenic defect of the extraocular muscle. The forced duction test is helpful in distinguishing between a neurogenic and a restrictive defect.

A 10-month-old boy had strabismus since birth. His birth weight was 3,000 g, after a normal gestation and delivery. He had not undergone any previous surgery. The patient's parents both had myopia, and there was no history of strabismus in the family.

On examination the child had a face turn to the left. Fixation with the right eye was steady, and his eyes could follow small objects. With his left eye, the patient had central fixation, and the eye was steady and could follow moving objects. The right eye was in an extreme position of abduction. There was limitation in elevation and depression of the right eye. On attempted adduction there was mild globe retraction of the right eye. No proptosis, enophthalmos, or blepharoptosis were noted. The left eye had normal ductions. The anterior segment and fundus were normal in both eyes. Pupillary reactions were normal. Cycloplegic refraction was +2.25 in both eyes. The forced duction test performed under general anesthesia disclosed restriction in adduction of the right eye; that is, the globe could not be moved beyond the midline. Elevation and depression were normal. Results of the forced duction test of the left eye were normal. On orbital computed tomographic scans the globe was shown in a full abduction position. No anomaly of the extraocular muscles was found, except for minimal thinness of the medial rectus muscle.

During surgery, while trying to engage the lateral rectus muscle through a conjunctival fornix incision, we found a fibrotic band. The band was 2.5 mm wide and was inserted in the sclera at the 9 o'clock meridian, approximately 1.0 mm from the corneoscleral limbus, and extended toward the orbital apex, parallel to and separated from the lateral rectus muscle (Figure). The band was cut at the corneoscleral limbus, and approximately 15.0 mm of the band was extirpated. Thereafter, results of the forced duction test were negative. The right lateral rectus muscle was recessed 6.0 mm. Postoperatively there was a residual right exotropia of 20 degrees. Ocular movements showed mild limi-

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

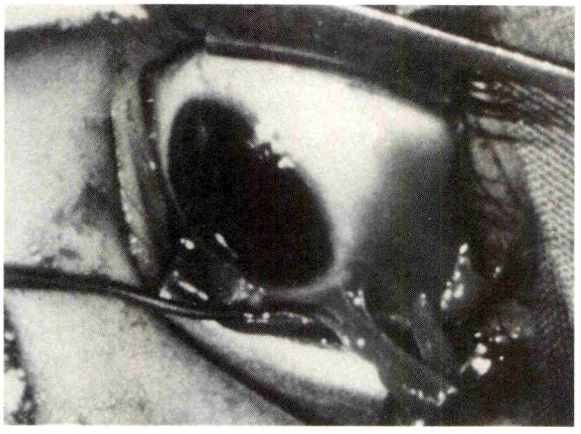


Figure (Spierer, Desatnik, and Barishak). Extraocular fibrous band inserted in the sclera adjacent to the corneoscleral limbus.

tation in adduction of the right eye with minimal limitation in elevation or depression.

Pathologic examination disclosed fibrous tissue, partially dense and partially loose, with sections of capillaries and peripheral nerves. No muscle tissue was noted as confirmed by Masson's trichrome and periodic acid-Schiff stains.

Our patient had a clinical course similar to that of a partial congenital oculomotor nerve paralysis in his right eye. Absence of adduction, elevation, and depression could have represented paralysis of the medial, superior, and inferior recti muscles, respectively. Positive results of the forced duction test on attempted adduction, however, were not consistent with an oculomotor nerve paralysis. The fibrous band found during surgery kept the eye at the extreme abducted position and caused retraction of the globe on attempted adduction. The positive results of the forced duction test were also explained by this aberrant band.

Spielman[2] described a patient with Duane's retraction syndrome in whom there was a vertical restriction in addition to horizontal ocular movement limitation. This was explained by the contraction on vertical gaze of the overly tight horizontal recti muscles. In our patient, the aberrant band could have pulled the eye tightly against the medial rectus muscle, thus keeping the globe in a restricted position that affected the vertical movements. Extirpating the fibrotic band significantly improved the horizontal as well as the vertical ocular movements.

In 1964, Goldstein[3] reported a similar case of congenital fibrous band. His patient underwent two surgical procedures to correct hypotropia and esotropia. Nevertheless, the patient was still unable to elevate the eye. During the third operation, three fibrous bands were identified approximately 15.0 mm from the corneoscleral limbus. The bands were inserted into the sclera, and their posterior ends disappeared into the back of the orbit. As in our case, no connection between the bands and the extraocular muscles was noted.

References

1. Duke-Elder, S., and Wybar, K. C.: Ocular Motility and Strabismus. In Duke-Elder, S. (ed.): System of Ophthalmology, vol. 6. St. Louis, C. V. Mosby, 1973, pp. 736–740.
2. Spielman, A.: Bilateral vertical retraction syndrome in horizontal bilateral Duane's syndrome. Graefes Arch. Clin. Exp. Ophthalmol. 226:425, 1988.
3. Goldstein, J. H.: The intraoperative forced duction test. Arch. Ophthalmol. 72:647, 1964.

Large Refractive Change After Strabismus Surgery

R. David Reynolds, M.D., Leonard B. Nelson, M.D., and Mark Greenwald, M.D.

Department of Pediatric Ophthalmology, Wills Eye Hospital, Thomas Jefferson Medical College (R.D.R., L.B.N.); and Department of Pediatric Ophthalmology, Children's Memorial Hospital, University of Illinois at Chicago (M.G.).

Inquiries to Leonard B. Nelson, M.D., Department of Pediatric Ophthalmology, Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

In 1936, Marshall[1] reported that 42 of 70 eyes (60%) operated on showed changes in refraction after strabismus surgery. More recent studies seem to confirm that significant refractive changes may occur, particularly with regard to astigmatism, but that these changes usually do not persist beyond the early postoperative period.[2,3] Fix and Baker[3] reported that only 3% of their patients had changes of at least 1 diopter of astigmatism at one year postoperatively. Most authors have attributed these refractive changes to a change in corneal astigmatism.[2] Kushner[4] has shown that oblique muscle surgery is often accompanied by a change in the

axis of astigmatism. We treated a patient with generalized fibrosis syndrome who had a significant and persistent change in refractive error after strabismus surgery.

A 2-week-old girl was first examined by a pediatric ophthalmologist (M.G.) because she had marked blepharoptosis. At that time, the patient had a +2.00 refraction bilaterally. She was reexamined on numerous occasions because of her marked blepharoptosis and chin-up posture, a generalized decrease in ocular movements with infraduction of the globes bilaterally, facial weakness, and difficulty with swallowing. At 2 years of age, cycloplegic refraction had progressed to R.E.: −16.00 +10.00 × 105 and L.E.: −16.00 +8.00 × 75. Repeat refraction measurement several weeks later was R.E.: −16.00 +8.00 × 90 and L.E.: −16.00 +8.00 × 90. The patient's refraction was independently measured by two additional pediatric ophthalmologists, and these measurements were nearly identical to the initial measurement. Because of the patient's significant chin-up posture and marked infraduction of the globes, she underwent bilateral inferior rectus muscle recession of 12 mm and total inferior rectus muscle disinsertion in each eye. Forced duction testing at the time of the initial operation disclosed significant restriction to elevation.

Repeat refraction measurements two months after the operation disclosed a refractive error of R.E.: −12.00 +5.00 × 100 and L.E.: −12.00 +5.00 × 90. Because of the marked change, refraction was again measured at four months and six months after the final operation. The myopia and astigmatic error had decreased to R.E.: −6.50 +1.50 × 90 and L.E.: −5.00 +2.00 × 105. One year later, visual acuity was 20/50 in each eye with this refraction.

The findings in our patient are unusual in the degree to which the refractive error changed after strabismus surgery. Whereas other authors have speculated that smaller, more transient changes in postoperative astigmatism are caused by eyelid swelling or by a change in the position of the eye relative to the eyelids, the findings in our patient seem to confirm that larger changes in astigmatism with their longer duration are likely to result from a variation in the force that the muscles exert on the globe.[2] In this case, the fibrotic and shortened inferior recti muscles appear to have been the cause of the corneal steepening at 90 degrees. The reversibility of the astigmatism after inferior rectus muscle disinsertion lends further support to these muscles being responsible for the preoperative astigmatism in this patient.

References

1. Marshall, D.: Changes in refraction following operation for strabismus. Arch. Ophthalmol. 15:1020, 1936.

2. Thompson, W. E., and Reinecke, R. D.: The changes in refractive status following routine strabismus surgery. J. Pediatr. Ophthalmol. Strabismus 17:372, 1980.

3. Fix, A., and Baker, J. D.: Refractive changes following strabismus surgery. Am. Orthoptic J. 35:59, 1985.

4. Kushner, B. J.: The effect of oblique muscle surgery on the axis of astigmatism. J. Pediatr. Ophthalmol. Strabismus 23:277, 1986.

Mean Visual Acuity

Jack T. Holladay, M.D., and Thomas C. Prager, Ph.D.

Department of Ophthalmology, Hermann Eye Center, University of Texas Medical School at Houston.

Inquiries to Jack T. Holladay, M.D., Hermann Eye Center, 6411 Fannin, Houston, TX 77030.

Calculating mean visual acuity on a series of patients has been done incorrectly in most studies, which leads to a significant overestimate or underestimate of the true mean visual acuity. The basic problem relates to the difference between the arithmetic and geometric mean of a set of numbers. For the correct mean visual acuity, calculating the geometric mean yields the proper value.

Modern visual acuity charts are designed so that the letter sizes on the chart follow a geometric progression (that is, advance in uniform steps on a logarithmic scale).[1] The International Council of Ophthalmology Committee on optotypes accepted the original recommendation of Green[2] to have the letter sizes change by 0.1-log unit steps, which is equivalent to letter sizes changing by a factor of 1.2589 between lines.[1] This standard led to the LogMAR (logarithm of the minimum angle of resolution) notation[1] as plotted in the Figure.

The letter sizes between 20/10 and 20/200 progress in a linear fashion on a logarithm scale, and visual performance midway between

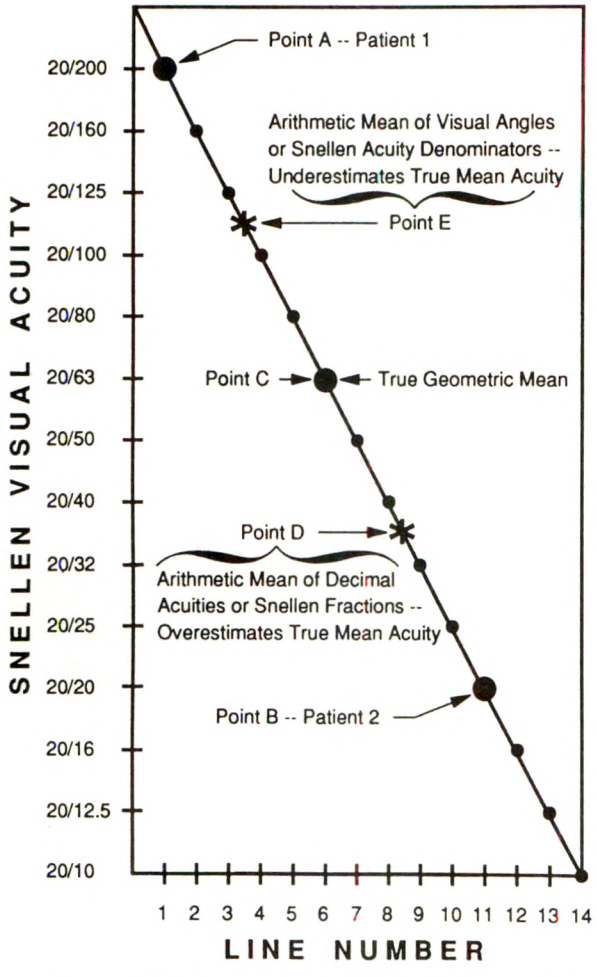


Figure (Holladay and Prager). The true geometric mean visual acuity between Patient 1 with visual acuity of 20/200 (Point A) and Patient 2 with visual acuity of 20/20 (Point B), is 20/63 (Point C). The incorrect arithmetic mean obtained by taking the average of the decimal visual acuities or Snellen fractions is 20/36 (Point D). The arithmetic mean obtained by taking the average of the Snellen visual acuity denominators or visual angles is 20/110 (Point E). Arithmetic means severely overestimate or underestimate the true geometric mean visual acuity.

20/200 (line 1) and 20/20 (line 11) is 20/63 (line 6) (Figure). This visual acuity of 20/63 is the geometric mean of these two visual acuities. Mathematically, the geometric mean is calculated by taking the logarithm of each of the sample values, determining the average of the logarithm values, then taking the antilogarithm of this average. In this example, the logarithm of 20/200 (point A in the Figure) is −1.0 and the log of 20/20 (point B in the Figure) is 0. The average would be −0.50, for which the antilogarithm is decimal 0.32 or a Snellen notation of 20/63 (point C in the Figure).

In our example, if we were to calculate the inappropriate arithmetic mean using the decimal values, as suggested most recently by Vila-Coro and Vila-Coro,[3] we would obtain an average decimal value of 0.55 ([0.1 + 1.0]/2) or 20/36 (point D in the Figure). This method overestimates the true geometric mean visual acuity and minimizes the contribution of the poor visual acuity samples.

A second incorrect method is to take the arithmetic mean of the minimum angle of resolution, which is equivalent to taking the average of the denominators of the Snellen notation. Pincus[4] used this method to determine the average visual acuity for a given refractive error. Using this incorrect method in our previous example, the mean visual acuity would have been 20/110 ([200 + 20]/2). This arithmetic method will severely underestimate the actual geometric mean visual acuity (point E in the Figure). If one takes the geometric mean of the Snellen denominators, the minimum visual angles of resolution, or the Snellen fractions or decimals, the result is the same, 20/63, which is the correct result.

Fortunately, with the newer visual acuity charts (for example, Bailey-Lovie, ETDRS, PERK) that have an equal number of letters on a line and a constant geometric progression between lines, the actual line numbers are directly proportional to the logarithm of the visual acuity, as we have shown previously.[5] When these charts are used, the geometric mean visual acuity is more simply obtained by calculating the arithmetic mean of the number of lines or letters correct, then converting the result to the corresponding Snellen visual acuity.[5] With many standard projector charts, however, in which the number of letters on each line are not equal or the progression is not consistent (for example, the 20/125 and 20/160 lines are missing and a 20/70 line should not be present), this simple method may not be used and the logarithmic method is necessary.

Likewise, when other statistical analyses are performed on visual acuity, such as correlation coefficients or standard deviations, they must be calculated using the logarithm of the visual acuity or logarithm of the visual angle as Sloan[6] has shown in her correlations of visual acuity with refractive error. Care should be taken by authors and reviewers to assure that these principles are followed so that mean visual acuity

presented in a study is valid and comparable to other studies. Unfortunately, many of the mean visual acuities in published reports have used one of the two incorrect arithmetic methods, which make most comparisons of mean visual acuity invalid.

References

1. Bailey, I. L., and Lovie, J. E.: New design principles for visual acuity letter charts. Am. J. Optom. Physiol. Optics. 53:740, 1976.
2. Green, J.: Notes on the clinical determination of the acuteness of vision including the construction and graduation of optotypes. Trans. Am. Ophthalmol. Soc. 10:644, 1905.
3. Vila-Coro, A. A., and Vila-Coro, An. A.: Mean visual acuity. Am. J. Ophthalmol. 107:564, 1989.
4. Pincus, M. H.: Unaided visual acuities correlated with refractive errors. Am. J. Ophthalmol. 29:853, 1946.
5. Holladay, J. T., and Prager, T. C.: Snellen equivalent for Bailey-Lovie acuity chart. Arch. Ophthalmol. 107:955, 1989.
6. Sloan, L. L.: Measurement of visual acuity. Arch. Ophthalmol. 45:704, 1951.

Infectious Crystalline Keratopathy After Relaxing Incisions

Marilyn C. Kincaid, M.D., Bradley D. Fouraker, M.D., and David J. Schanzlin, M.D.

Bethesda Eye Institute, Departments of Ophthalmology (M.C.K., B.D.F., D.J.S.) and Pathology (M.C.K.), St. Louis University School of Medicine.

Inquiries to Marilyn C. Kincaid, M.D., Bethesda Eye Institute, 3655 Vista Ave., St. Louis, MO 63110.

Infectious crystalline keratopathy is characterized clinically by a branching, crystalline infiltrate within corneal stroma, with minimal or no inflammation, and no necrosis or edema.[1] In a patient described by Gorovoy and associates,[1] the diagnosis of a bacterial infiltrate was not made until the cornea was examined histologically. Many of these cases have occurred after penetrating keratoplasty. It would seem reasonable that the deep, but not perforating, incisions made in the cornea for keratorefractive purposes might also inadvertently become colonized in a similar manner.

A 75-year-old woman underwent penetrating keratoplasty in the left eye for aphakic bullous keratopathy in July 1989. Postoperative visual acuity was poor because of residual astigmatism, reduced somewhat by selective suture removal by photokeratoscopy. However, 11 diopters of astigmatism remained, with the steep meridian at 150 degrees. In May 1990, two relaxing incisions were placed by the method described by Lindquist.[2] The patient was given 1% prednisone eyedrops four times per day, and visual acuity improved to 20/70. Three months after this procedure, rounded crystalline-appearing infiltrates were seen on both sides of one of the incisions (Fig. 1). Visual acuity had decreased to 20/300. She was treated with tobramycin/dexamethasone eyedrops every two hours for 72 hours, with slight improvement in vision. The antibiotic was then changed to chloramphenicol.

The patient underwent repeat penetrating keratoplasty. The corneal button was placed in routine 10% buffered formalin for light microscopy. Both of the relaxing incisions were identified, and the button was bisected perpendicular to these incisions.

Microscopically, corneal epithelium lined the entire depth of one incision. The opposite incision was partially lined by epithelium. Gram-positive cocci were present within stroma adjacent to the epithelial lining for almost the entire depth of the opposite incision, corresponding to the infiltrates seen clinically. The bacteria also extended away from the incision edges within pre-Descemet's stroma (Fig. 2).

More than 17 cases of infectious crystalline

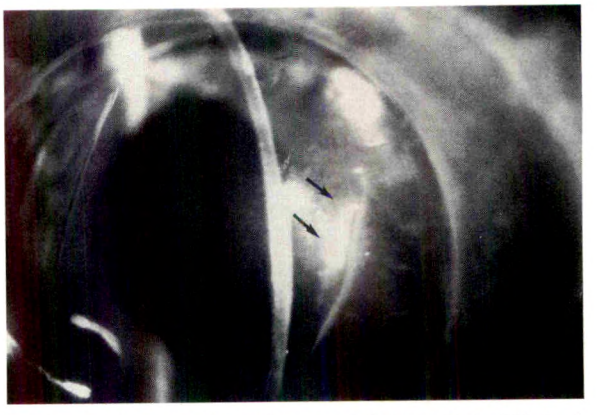


Fig. 1 (Kincaid, Fouraker, and Schanzlin). Clinical appearance of the infiltrate (arrows) along one of the relaxing incisions. The other incision is free of infiltrates.

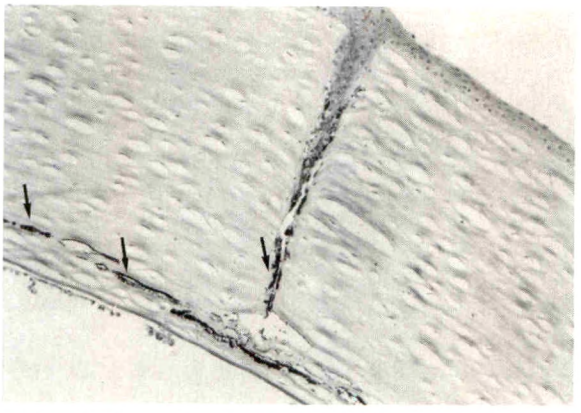


Fig. 2 (Kincaid, Fouraker, and Schanzlin). Microscopic appearance of the bacteria along the incision vertically and extending horizontally in the pre-Descemet's area (arrows) (Brown-Brenn, ×156).

keratopathy, a term coined by Meisler and associates,[3] have been reported. Most have been various species of bacteria, but in two cases, fungi were demonstrated that responded to appropriate therapy.[4] Two factors seem to be common to the cases: an epithelial defect, usually from a surgical incision or site of a suture; and immunosuppression, most often from intensive topical corticosteroid therapy. The infectious agent apparently gains entrance through the epithelial defect and remains within stroma even after the defect has healed.

Both of these factors were noted in our patient. The relaxing incisions, according to usual procedure, were not sutured. The patient had continued the corticosteroid eyedrops from the time the incisions were made. Careful follow-up to recognize infection as early as possible in these patients may allow conservative therapy. If the infiltrate increases in size despite appropriate antibiotics, however, penetrating keratoplasty is usually required.

References

1. Gorovoy, M., Stern, G., Hood, C., and Allen, C.: Intrastromal noninflammatory bacterial colonization of a corneal graft. Arch. Ophthalmol. 101:1749, 1983.

2. Rowsey, J., and Rubin, M.: Refraction problems after refractive surgery. Surv. Ophthalmol. 32:414, 1988.

3. Meisler, D. M., Langston, R. H. S., Naab, T. J., Aaby, A. A., McMahon, J. T., and Tubbs, R. R.: Infectious crystalline keratopathy. Am. J. Ophthalmol. 97:337, 1984.

4. Weisenthal, R. W., Krachmer, J. H., Folberg, R., Dunn, S. P., and Whitson, W. E.: Postkeratoplasty crystalline deposits mimicking bacterial infectious crystalline keratopathy. Am. J. Ophthalmol. 105:70, 1988.

Immunofluorescence Findings in Pseudopemphigoid Induced by Short-term Idoxuridine Administration

Israel Kremer, M.D., Daniel Rozenbaum, M.D., and Eliezer Aviel, M.D.

Departments of Ophthalmology, Beilinson Medical Center, and Sackler School of Medicine, Tel Aviv University (I.K.), and Barzilai Hospital (D.R., E.A.).

Inquiries to Israel Kremer, M.D., Department of Ophthalmology, Beilinson Medical Center, Petah Tiqva 49100, Israel.

Drug-induced cicatricial pemphigoid has been reported after long-term topical administration of several medications.[1,2] The clinical and microscopic findings in pseudopemphigoid are similar to ocular cicatricial pemphigoid.[2,3] Rarely have intercellular immunoglobulins been found in the conjunctival epithelium of both pseudopemphigoid and cicatricial pemphigoid.[1] We treated a patient with pseudopemphigoid after short-term idoxuridine therapy.

A 36-year-old man had been treated eight years previously with idoxuridine eyedrops for two weeks because of herpetic keratitis in the left eye. One year later, the patient developed recurrent conjunctival erosions, conjunctival scarring, and trichiasis. On examination, visual acuity was 20/20 and intraocular pressure was 16 mm Hg in each eye. Results of slit-lamp examination of the right eye were unremarkable, but examination of the left eye disclosed trichiasis, symblepharon, and conjunctival scarring. Breakup time was abnormal (four seconds), and conjunctival rose bengal staining was noted.

Two snip biopsy specimens were taken from the inferior fornix conjunctiva of each eye. One was processed routinely for histopathologic examination, and the second was frozen. Cryostat sections were tested for immunoglobulins, complement, albumin, properdin, and fibrinogen.

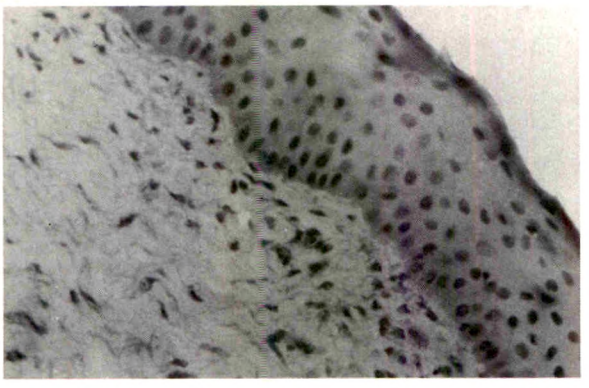


Fig. 1 (Kremer, Rozenbaum, and Aviel). Light microscopy of the left inferior fornix conjunctiva showing complete absence of goblet cells, squamous epithelial metaplasia, subepithelial fibrosis, and mild chronic inflammation (hematoxylin and eosin, × 250).

The right conjunctiva was normal, whereas the affected left conjunctiva showed a complete absence of goblet cells, squamous metaplasia, subepithelial fibrosis, and mild chronic inflammation (Fig. 1). No immunoglobulins were found along the basement membrane with immunofluorescent examination. Epithelial intercellular staining was found for IgG (Fig. 2, left), IgA, complement 3, albumin (Fig. 2, right), and fibrinogen. Staining was negative for IgD, IgE, properdin, and complement 4 and 19. We did not detect circulating anticonjunctival antibodies.

Pseudopemphigoid induced by long-term local drug administration was first described by Patten, Cavanagh, and Allansmith.[1] Fiore, Jacobs, and Goldberg[2] found that it may be a self-limiting disease or may progress to conjunctival scarring and epidermalization despite medication withdrawal and corticosteroid treatment. They proposed that it represents a spectrum of diseases, ranging from a self-limiting toxic form to progressive autoimmune phenomenon.

The immunohistochemical results vary in different reports,[1-3] including immunoglobulin staining of the basement membrane, subepithelial plasma cells, or both. Intercellular immuno-

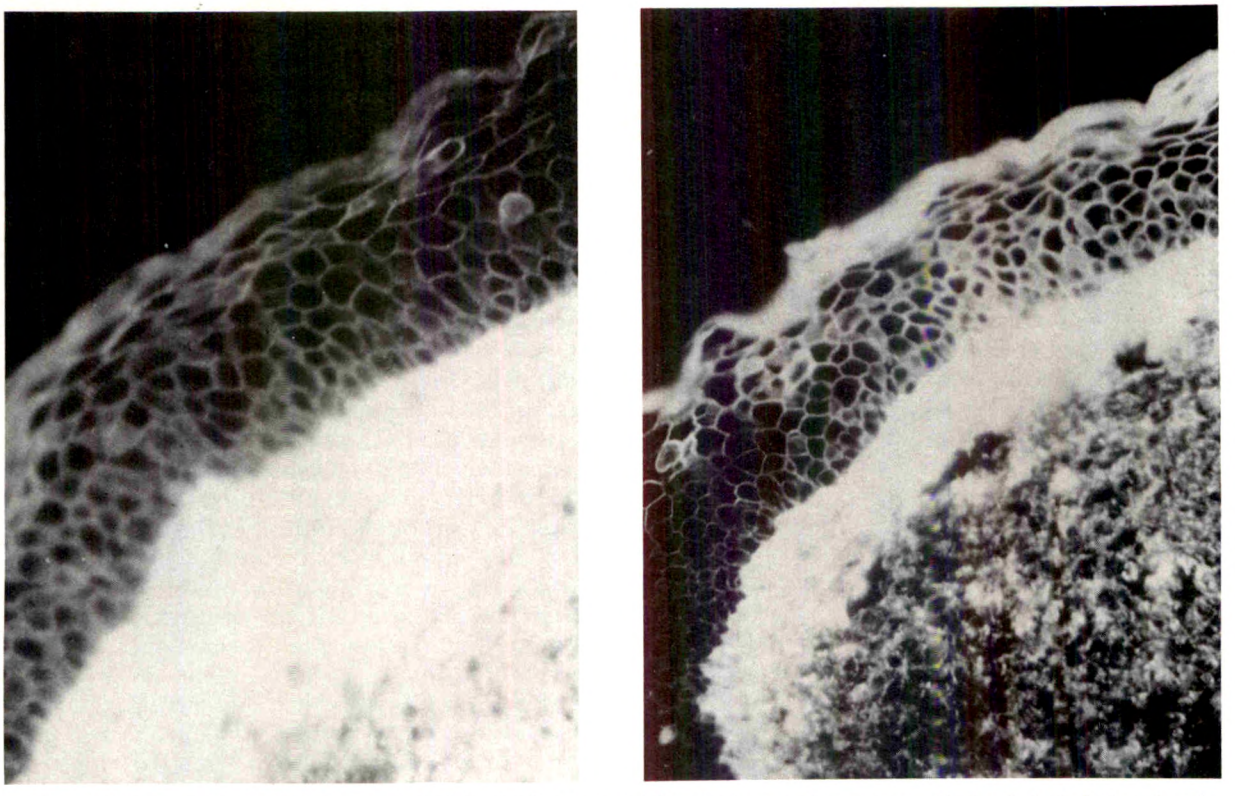


Fig. 2 (Kremer, Rozenbaum, and Aviel). Left, Immunofluorescent microscopy of the left inferior fornix conjunctiva showing intraepithelial intercellular staining for IgG (immunofluorescent anti-IgG staining, × 250). Right, Immunofluorescent microscopy of the left inferior fornix conjunctiva showing intraepithelial intercellular staining for albumin. The subepithelial wide band of fluorescence is a nonspecific finding (immunofluorescent anti-albumin staining, × 250).

globulins have rarely been reported.[1]

Lass, Thoft, and Dohlman[5] reported irreversible conjunctival cicatrization after long-term idoxuridine therapy. Results of immunofluorescence were negative or nonspecific, and no circulating autoantibodies were detected. They maintained that pseudophemphigoid has no immunologic basis but rather is a toxic reaction.

The epithelial intercellular immunoglobulin staining found in our patient after short-term idoxuridine administration may indicate an immunologic mechanism. As idoxuridine is nonselectively activated in normal epithelial cells, it may disrupt DNA synthesis, after which the cell membrane becomes immunogenic. Additionally, chemical injury of the surface epithelium by iodine may change its antigenic properties. The absence of circulating autoantibodies may indicate that pseudopemphigoid is a local autoimmune disease, in addition to its toxic aspect.

References

1. Patten, J. T., Cavanagh, H. D., and Allansmith, M. R.: Induced ocular pseudopemphigoid. Am. J. Ophthalmol. 82:272, 1976.

2. Fiore, P. M., Jacobs, I. H., and Goldberg, D. B.: Drug-induced pemphigoid. A spectrum of diseases. Arch. Ophthalmol. 105:1660, 1987.

3. Pouliquen, Y., Patey, A., Foster, C. S., Goichot, L., and Savoldelli, M.: Drug-induced cicatricial pemphigoid affecting the conjunctiva. Light and electron microscopic features. Ophthalmology 93:775, 1986.

4. Lass, J. H., Thoft, R. A., and Dohlman, C. H.: Idoxuridine-induced conjunctival cicatrization. Arch. Ophthalmol. 101:747, 1983.

Keratoconjunctivitis Sicca Caused by Diphenoxylate Hydrochloride With Atropine Sulfate (Lomotil)

Thomas H. Mader, M.D., and R. Doyle Stulting, M.D.

Department of Ophthalmology, Emory University School of Medicine. This study was supported in part by a departmental grant from Research to Prevent Blindness, Inc., and by P30 EY06360, a National Institutes of Health departmental core grant.

Inquiries to R. Doyle Stulting, M.D., Emory Eye Center, 1327 Clifton Rd. N.E., Atlanta, GA 30322.

Systemically administered antimuscarinics can cause decreased aqueous tear secretion from the lacrimal gland, which is innervated by parasympathetic fibers of the seventh cranial nerve.[1-3] Subcutaneous administration of atropine sulfate markedly reduced tear production in dogs[4] and cats.[1] In humans, subcutaneous injection of atropine sulfate (1 mg) decreased lacrimal secretion by almost 50%,[2] and oral atropine sulfate (1 to 2 mg) reduced tear production from 15 μl/minute to 3 μl/minute.[3] We treated a patient with keratoconjunctivitis sicca caused by high doses of diphenoxylate hydrochloride with atropine sulfate (Lomotil).

A 47-year-old man had undergone a gastrectomy and vagotomy for a perforated duodenal ulcer in 1968. The postoperative course was complicated by severe chronic diarrhea that was unresponsive to surgical intervention and could only be controlled by daily medication containing 25 to 75 mg of diphenoxylate hydrochloride combined with 0.25 to 0.75 mg of atropine sulfate (ten to 30 tablets). To discourage deliberate overdosage, atropine is added to the active narcotic, diphenoxylate.

In the mid-1980s, the patient noted the gradual onset of ocular irritation, burning, photophobia, and injection. Examination disclosed a decreased tear meniscus and punctate epithelial keratopathy. A diagnosis of tear deficiency was made, but treatment with artificial tears and punctal occlusion was unsuccessful. The condition worsened, and on several occasions large epithelial defects that were attributed to tear deficiency appeared spontaneously. With oral supplementation, vitamin A levels were within normal limits.

To investigate the possibility that diphenoxylate hydrochloride with atropine sulfate exacerbated the tear deficiency, we initiated a course of therapy with atropine sulfate–free diphenoxylate hydrochloride obtained from the manufacturer. Within 48 hours, there was a dramatic improvement in symptoms and resolution of the corneal abnormalities. During the next four months, the patient's regimen was switched from the atropine sulfate–containing drug to the atropine sulfate–free drug four times. Each time, there was a significant subjective and objective improvement on the atropine sulfate–free preparation.

Schirmer's test (five minutes without anesthesia) was performed on four occasions when the patient was taking 20 tables daily of diphenoxylate hydrochloride with atropine sulfate and on four occasions when he was taking 20 tablets daily of diphenoxylate hydrochloride without atropine sulfate. All tests were performed by the same observer at the same time of day. Results for the right eye were 0.25 ±

0.14 mm and 2.25 ± 0.83 mm with and without atropine sulfate, respectively. Results for the left eye were 0.0 ± 0.0 mm and 1.25 ± 0.59 mm with and without atropine sulfate, respectively. The difference between eyes was not significant, but the difference between measurements with and without atropine sulfate was significant ($P < .01$, analysis of variance).

The dosage of medication required by our patient (ten to 30 tablets per day containing 0.25 to 0.75 mg of atropine sulfate) was higher than the maximum recommended dosage (eight tablets per day), and the duration of treatment was unusually long. The Schirmer's test result when the patient did not take atropine sulfate–containing tablets was also abnormal, suggesting that the patient might have an underlying tear disorder. Nevertheless, the use of diphenoxylate hydrochloride with atropine sulfate was clearly associated with the signs and symptoms of severe keratoconjunctivitis sicca.

The findings in this patient demonstrate that diphenoxylate hydrochloride with atropine sulfate can cause severe keratoconjunctivitis sicca in susceptible individuals. It also emphasizes the need to obtain a complete history of systemic medications when examining patients with tear deficiency.

References

1. Arnett, B. D., Brightman, A. H., II, and Musselman, E. E.: Effect of atropine sulfate on tear production in the cat when used with ketamine hydrochloride and acetylpromazine maleate. J. Am. Vet. Med. Assoc. 185:214, 1984.

2. Balik, J., and Hradecky, F.: Effect of atropine and pilocarpine on the secretion of chloride ion into the tears. Cesk. Oftalmol. 14:28, 1958.

3. Erickson, O. F.: Drug influences on lacrimal lysozyme production. Stanford Med. Bull. 18:34, 1960.

4. Vestre, W. A., Brightman, A. H., II, Helper, L. C., and Lowery, J. C.: Decreased tear production associated with general anesthesia in the dog. J. Am. Vet. Med. Assoc. 174:1006, 1979.

The Oculocardiac Reflex During Enucleation

Paul M. Munden, M.D., Keith D. Carter, M.D., and Jeffrey A. Nerad, M.D.

Department of Ophthalmology, University of Iowa Hospitals and Clinics.

Inquiries to Keith D. Carter, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

Cardiac arrhythmias generated by the oculocardiac reflex are well-known complications of ocular surgery.[1] Traction on the extraocular or eyelid muscles, compression of the globe, intraocular and retrobulbar injection, iris traction, and retinal reattachment surgery are procedures that can induce the oculocardiac reflex.[1-3] Previous reports have emphasized the association between extraocular muscle traction during enucleation procedures and the induction of cardiac arrhythmias.[1-3] We performed enucleations on the eyes of three patients who developed transient cardiac arrhythmias during clamping of the optic nerve.

Case 1

A 9-year-old boy, who underwent lensectomy and anterior vitrectomy at 5 weeks of age for persistent hyperplastic primary vitreous, had a blind, painful right eye. The right eye was enucleated under general anesthesia. Atropine, 0.2 mg, was given intravenously before intubation. Upon clamping of the optic nerve, the patient had an eight-beat run of bigeminy, which resolved spontaneously. The optic nerve was cut and cauterized, and pressure was applied over the orbital contents. Additional beats of bigeminy were noted with the pressure. The arrhythmias resolved spontaneously without hemodynamic compromise.

Case 2

A 47-year-old woman with malignant melanoma of the left eye underwent an enucleation under general anesthesia. Atropine, 0.4 mg, was given intramuscularly before intubation. Upon clamping the optic nerve, transient atrioventricular disassociation and frequent premature ventricular complexes were noted. Glycopyrrolate, 0.2 mg, was given intravenously for sinus bradycardia and the nodal rhythm. The arrhythmias resolved without hemodynamic compromise.

Case 3

A 24-year-old man with malignant melanoma of the left eye underwent an enucleation under general anesthesia. Upon clamping the optic nerve, the patient developed a sinus bradycardia at a rate of 47 beats per minute.

Atropine, 0.8 mg, was given intravenously with the heart rate returning to normal and no hemodynamic compromise.

All patients were discharged from the hospital the following day without evidence of postoperative complications.

Sinus tachycardia, ectopic beats, bidirectional junctional tachycardia, and bradycardia have been reported during enucleation procedures performed under general anesthesia in association with traction on the extraocular muscles.[3] Our patients developed arrhythmias upon clamping of the optic nerve, a time at which all extraocular muscles have been severed from the globe and are under no traction.

The afferent limb of the oculocardiac reflex is thought to travel through sensory branches of the ophthalmic nerve to terminate at the main sensory nucleus of the trigeminal nerve. The efferent arc travels by the vagus nerve to the heart, which produces slowing of the sinus rhythm and depression of the intracardiac conduction system.[4] Each of the three divisions of the trigeminal nerve sends sensory branches to the dura mater.[5] It is possible that traction on the optic nerve sheath or the trauma of the clamping procedure initiated the oculocardiac reflex in these patients.

Our patients were relatively young and in good health, and their cardiac arrhythmias resolved without hemodynamic compromise. Pharmacologic intervention, however, was necessary in two of the patients. Surgeons and anesthesiologists should be aware of this potentially fatal complication during enucleation procedures.

References

1. Berler, D. K.: The oculocardiac reflex. Am. J. Ophthalmol. 56:954, 1963.

2. Pontinen, P. J.: The importance of the oculocardiac reflex during ocular surgery. Acta Ophthalmol. 86:7, 1966.

3. Alexander, J. P.: Reflex disturbances of cardiac rhythm during ophthalmic surgery. Br. J. Ophthalmol. 59:518, 1975.

4. Walsh, F. B., and Hoyt, W. F.: Clinical Neuro-Ophthalmology, ed. 3, vol. 1. Baltimore, Williams and Wilkins, 1969, pp. 379–382.

5. Anderson, J. E.: Grant's Atlas of Anatomy, ed. 7, chap. 8. Baltimore, Williams and Wilkins, 1979, p. 5.

Endogenous *Candida* Species Endophthalmitis Associated With Increased Levels of D-Arabinitol in Serum and Vitreous

Seiji Hayasaka, M.D., Sachiko Noda, M.D., and Tomoichi Setogawa, M.D.

Department of Ophthalmology, Shimane Medical University.

Inquiries to Seiji Hayasaka, M.D., Department of Ophthalmology, Shimane Medical University, Izumo, Shimane 693, Japan.

D-arabinitol, a major metabolite of *Candida* species, has been reported to have increased levels in sera of patients with invasive candidiasis.[1-3] We examined D-arabinitol values in the sera and vitreous by the enzymatic fluorometric method of Soyama and Ono.[2,4]

A 2.0-ml aliquot of peripheral blood was obtained from a cubital vein, and the serum was separated. A 0.3-ml sample of vitreous was aspirated with a 23-gauge needle through sclera 4 mm from the corneoscleral limbus; 0.2 ml was analyzed for cytologic and microbiologic study and 0.1 ml was used for D-arabinitol and creatinine assays.

A 61-year-old woman underwent total pancreatectomy for pancreas head carcinoma in April 1989. Postoperatively, her blood glucose level fluctuated, and she received intravenous hyperalimentation. In July 1990, the patient had high fever and blurred vision in the right eye. Visual acuity was R.E.: 20/200. A white fluffy exudative lesion associated with cells was found in the right fundus. An aliquot of vitreous was aspirated from the right eye. Cytologic study showed many polymorphonuclear leukocytes but no microorganisms. The D-arabinitol level was 10.2 μmol/l in the serum (normal, 4.4 ± 3.1 μmol/l) and 26.5 μmol/l in the vitreous. *Candida albicans* grew from the tip of the intravenous hyperalimentation catheter. Drip infusion of miconazole was given. Vitrectomy was performed in the right eye. No bacteria or fungi were found. In late August 1990, the white lesion in the fundus disappeared, and visual acuity in the right eye improved to 20/25. The D-arabinitol level in the serum decreased to 4.8 μmol/l.

Sera and vitreous of two patients with no ocular infection served as controls. A 65-year-old woman with idiopathic vitreous opacities in the left eye had 4.8 μmol/l of D-arabinitol in

the serum and an undetectable level of the metabolite in the vitreous. A 60-year-old man with complicated retinal detachment in the left eye had 2.4 μmol/l of D-arabinitol in the serum and an undetectable level of the metabolite in the vitreous.

Isolation of the fungi from ocular tissues confirms the diagnosis of *Candida* species endophthalmitis. It is not always possible to detect the fungus, however, even in clinically certain cases. In Japan, 59 patients with clinically certain endogenous *Candida* species endophthalmitis had been described during the 13-year period between 1976 and 1988.[5] Among them, only 11 of 59 patients (19%) had positive cultures from the ocular tissues, whereas 48 patients (81%) had negative cultures from the eye but positive detection from the blood or the tip of a catheter.[5] Thus, the diagnosis of endogenous *Candida* species endophthalmitis is not easy to confirm.

Increased serum levels of D-arabinitol, a major metabolite of *Candida* species, is helpful for confirming the diagnosis of invasive candidiasis.[1-3] A high D-arabinitol/creatinine ratio in the serum has been recommended for the diagnosis.[2] The level of D-arabinitol in the serum of our patient was higher than in normal control patients but was not conclusive for a diagnosis of *Candida* species endophthalmitis. The D-arabinitol level in the vitreous of our patient was higher than in the serum. D-arabinitol concentrations in the vitreous of the control patients were less than those in the sera. *Candida* species might have been biochemically active in the right vitreous in our patient.

We believe that the determination of increased levels of D-arabinitol in the vitreous may be useful for the diagnosis of *Candida* species endophthalmitis.

References

1. Kiehn, T. E., Bernard, E. M., Gold, J. W. M., and Armstrong, D.: Candidiasis. Detection by gas-liquid chromatography of D-arabinitol, a fungal metabolite, in human serum. Science 206:577, 1979.

2. Soyama, K., and Ono, E.: D-arabinitol concentrations and D-arabinitol/creatinine ratios in serum obtained from the patients with invasive candidiasis. Rinsho Byori 35:1039, 1987.

3. Wong, B., and Brauer, K. L.: Enantioselective measurement of fungal D-arabinitol in the sera of normal adults and patients with candidiasis. J. Clin. Microbiol. 26:1670, 1988.

4. Soyama, K., and Ono, E.: Enzymatic fluorometric method for the determination of D-arabinitol in serum by initial rate analysis. Clin. Chim. Acta 149:149, 1985.

5. Katayama, T., Suruki, T., Kameda, Y., Egi, K., Fujiwara, H., Goto, S., and Mizushima, M.: *Candida* endophthalmitis. Folia Ophthalmol. Jpn. 40:181, 1989.

Unilateral Manifestation of the Vogt-Koyanagi-Harada Syndrome in a 7-year-old Child

David J. Forster, M.D., Ronald L. Green, M.D., and Narsing A. Rao, M.D.

Doheny Eye Institute, and Department of Ophthalmology, University of Southern California School of Medicine.

Inquiries to Narsing A. Rao, M.D., Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

Vogt-Koyanagi-Harada syndrome consists of panuveitis in association with neurologic or cutaneous manifestations.[1-4] The ocular findings consist of iridocyclitis, cellular vitreous infiltrate, serous retinal detachment, and disk hyperemia. These findings are typically bilateral but may be asymmetric in their degree of severity. Most patients are in their 20s to 50s.[4] We treated a child with Vogt-Koyanagi-Harada syndrome, in whom, on clinical and fluorescein angiographic examination, the findings were unilateral.

A 7-year-old Hispanic boy had a three-week history of redness, pain, and decreased vision in the right eye. The patient also had headaches, neck stiffness, and dysacusis. There was no history of trauma or previous ocular surgery, and there was no evidence of alopecia, vitiligo, or poliosis.

Visual acuity at the time of manifestation was R.E.: counting fingers at 2 feet and L.E.: 20/20. Pupillary responses were normal. On slit-lamp examination, the right eye showed moderate conjunctival injection, severe cell and flare in the anterior chamber, and moderate vitreous cells. The anterior segment and vitreous cavity were normal in the left eye, with no evidence of cellular infiltration. Ophthalmoscopic examination of the right eye disclosed moderate disk hyperemia, as well as posterior and inferior serous retinal detachments. Results of ophthal-

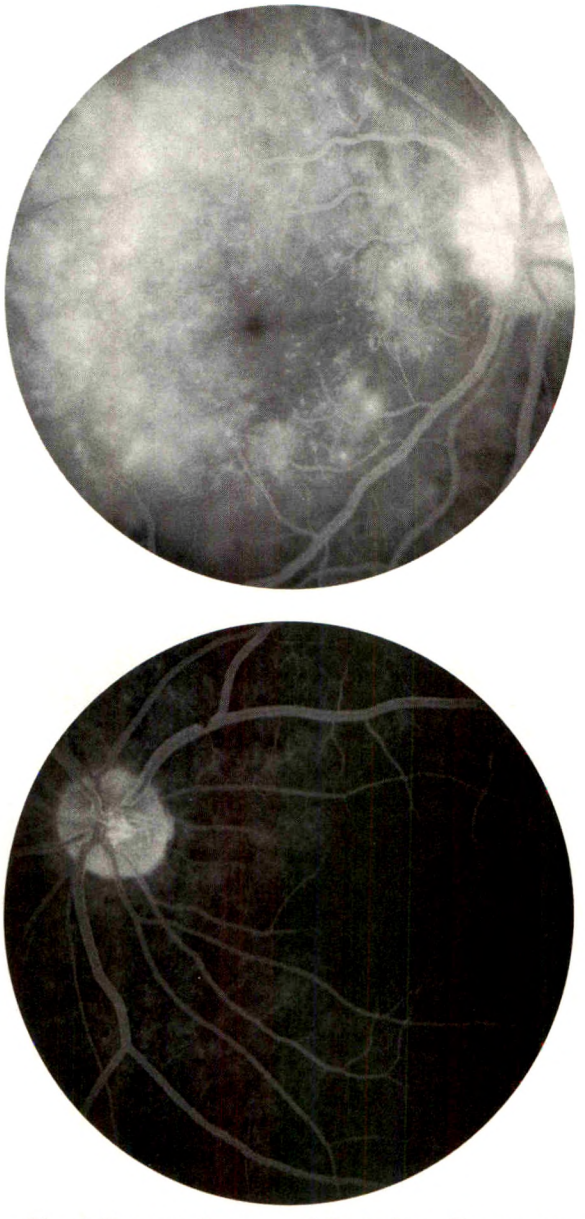


Fig. 1 (Forster, Green, and Rao). Top, Fluorescein angiogram of the right eye demonstrating staining of the disk, pinpoint areas of hyperfluorescence at the level of the retinal pigment epithelium, and pooling of dye in areas of serous retinal detachment temporal to the macula. Bottom, Normal angiogram of the left eye.

moscopic examination of the left eye were within normal limits, with no evidence of disk hyperemia or serous retinal detachment.

Fluorescein angiography (Fig. 1) demonstrated features typical of the Vogt-Koyanagi-Harada syndrome in the right eye (multiple pinpoint areas of hyperfluorescence at the level

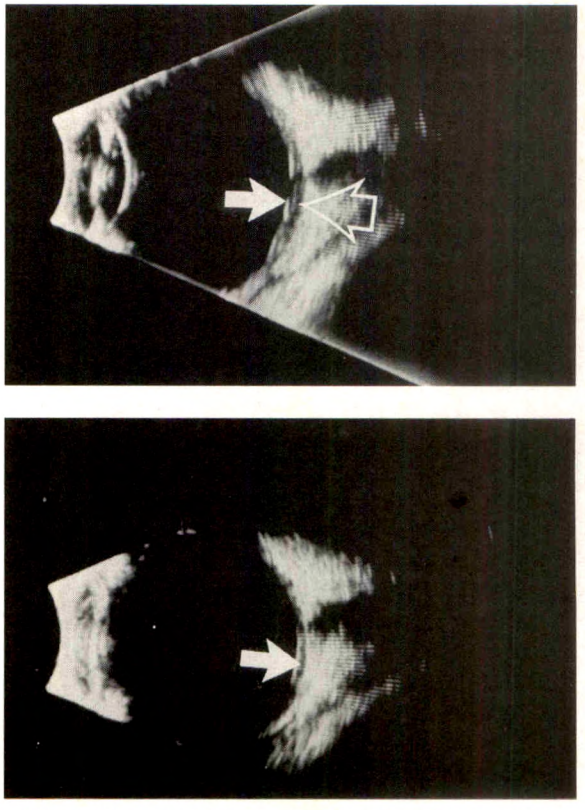


Fig. 2 (Forster, Green, and Rao). Top, B-scan ultrasonography of the right eye demonstrating diffuse choroidal thickening (open arrow), most marked in the peripapillary area, as well as overlying serous retinal detachment (solid arrow). Bottom, B-scan ultrasonography of the left eye demonstrating mild thickening of the choroid posteriorly (arrow).

of the retinal pigment epithelium, staining of the optic disk, and pooling of dye in the areas of serous retinal detachment), whereas the left eye showed none of these findings. Echographic examination (Fig. 2), however, disclosed diffuse bilateral medium reflective choroidal thickening, greater in the right eye than in the left eye, which was most marked in the peripapillary area and thinned out toward the periphery. The serous retinal detachments in the right eye were also noted on ultrasound examination. These echographic findings are typical of the Vogt-Koyanagi-Harada syndrome.[5]

The patient was treated with oral prednisone, 40 mg/day, with prompt resolution of the serous retinal detachments and clearing of the intraocular inflammation in the right eye. The corticosteroids were tapered over several weeks. Three months after manifestation, visual acuity was R.E.: 20/25 and L.E.: 20/20, and

the left eye continued to show no sign of intraocular inflammation.

This case is unusual in several respects. On clinical as well as fluorescein angiographic examination, there was evidence of unilateral involvement only. This manifestation is atypical, as there is almost always bilateral, albeit sometimes asymmetric, involvement with this syndrome. Bilateral involvement was detected, however, on ultrasound examination, demonstrating the usefulness of this technique in the diagnosis of this disease.

Also of interest was the young age of the patient. Most patients with Vogt-Koyanagi-Harada syndrome are between 20 and 50 years of age,[4] and the disease is rare in children. The patient met the diagnostic criteria for the Vogt-Koyanagi-Harada syndrome.[5] The absence of dermatologic manifestations was not surprising, as these may not become evident until later in the disease process and appear to be less common in Hispanic patients than in other ethnic groups.[5]

Other diagnostic possibilities were excluded by echography or by the clinical course. Posterior scleritis generally shows high-reflective choroidal thickening on echographic examination. Leukemic infiltration would be expected to recur as the corticosteroids were tapered. Uveal effusion syndrome typically shows minimal or absent intraocular inflammation. Reactive lymphoid hyperplasia affects middle-aged and older individuals.

Ophthalmologists should be aware of such atypical manifestations of the Vogt-Koyanagi-Harada syndrome. Although the disease is bilateral, it can, in rare cases, occur as a unilateral process, and may occur in younger individuals as well.

References

1. Vogt, A.: Frühzeitiges Ergrauen der Zilien und Bemerkungen über den sogenannten plötzlichen Eintritt dieser Veränderung. Klin. Monatsbl. Augenheilkd. 45:228, 1906.

2. Koyanagi, Y.: Dysakusis, Alopecia und Poliosis bei schwerer Uveitis nicht traumatischen Ursprungs. Klin. Monatsbl. Augenheilkd. 82:194, 1929.

3. Harada, E.: Clinical study of non-suppurative choroiditis. A report of acute diffuse choroiditis. Acta Soc. Ophthalmol. Jpn. 30:351, 1926.

4. Sugiura, S.: Vogt-Koyanagi-Harada disease. Jpn. J. Ophthalmol. 22:9, 1978.

5. Forster, D. J., Cano, M. R., Green, R. L., and Rao, N. A.: Echographic features of the Vogt-Koyanagi-Harada syndrome. Arch. Ophthalmol. 108:1421, 1990.

Changes in Corneal Curvature at Different Excimer Laser Ablative Depths

Kevin L. Litwin, B.A., Hamilton Moreira, M.D., Camiar Ohadi, B.A., and Peter J. McDonnell, M.D.

Doheny Eye Institute, Department of Ophthalmology, University of Southern California School of Medicine.

Inquiries to Peter J. McDonnell, M.D., Doheny Eye Institute, 1355 San Pablo St., Los Angeles, CA 90033.

The 193-nm excimer laser has been reported to remove precisely opaque anterior corneal tissue,[1] but the depth to which ablation can be performed safely has not been determined. With excimer laser surface photoablation on corneas of human cadaver eyes, we have observed a consistent corneal flattening after ablating to depths of 50 and 100 μm in two consecutive steps. With ablations of 150 μm, however, we observed an increase in corneal power. The photoablation was performed on four fresh human cadaver eyes within 48 hours of death. The corneas were free of any observable abnormalities and obvious edema. Intraocular pressure was maintained at 20 mm Hg throughout the experiment by a cannula inserted through the optic nerve. Intraocular pressure was confirmed to be between 19 and 21 mm Hg with a tonometer. Three photoablative steps were performed on each de-epithelialized cornea with an ablation zone diameter of 5.5 mm, using an excimer laser. Tonometry, pachymetry, and keratometry measurements and photokeratoscopy were performed before ablation and recorded after each 50-μm ablative step. The fluence was maintained at 160 mJ/cm^2 for each ablation, and the depth per pulse was 0.3 μm. The phototherapeutic protocol was used, with no refractive change intended. Consecutive photokeratoscopic pictures of the ablated corneas were used to assess qualitatively and quantitatively the amount of change in anterior corneal curvature.

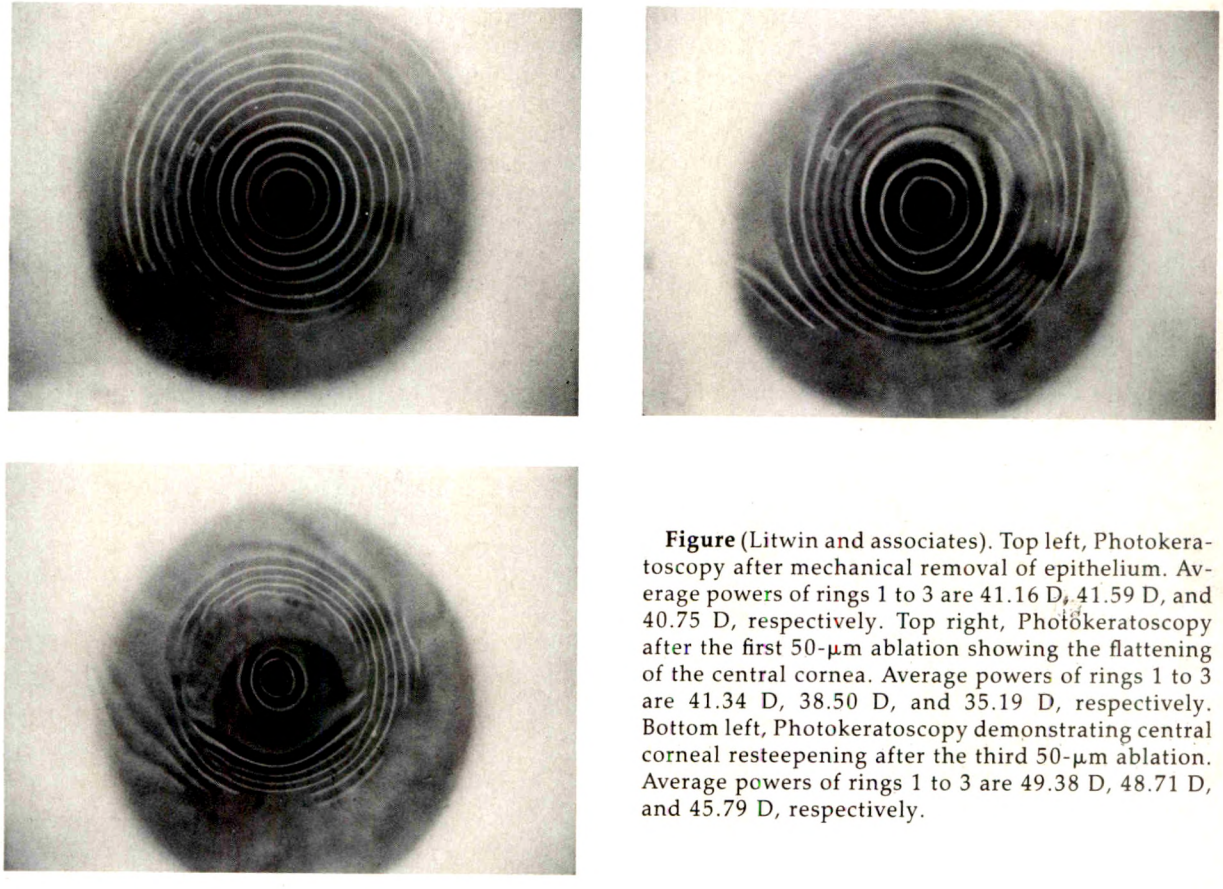


Figure (Litwin and associates). Top left, Photokeratoscopy after mechanical removal of epithelium. Average powers of rings 1 to 3 are 41.16 D, 41.59 D, and 40.75 D, respectively. Top right, Photokeratoscopy after the first 50-μm ablation showing the flattening of the central cornea. Average powers of rings 1 to 3 are 41.34 D, 38.50 D, and 35.19 D, respectively. Bottom left, Photokeratoscopy demonstrating central corneal resteepening after the third 50-μm ablation. Average powers of rings 1 to 3 are 49.38 D, 48.71 D, and 45.79 D, respectively.

No difference in corneal curvature was evident preoperatively in corneas as a result of mechanical removal of epithelium (Figure, top left). Corneal curvature differences were seen only after ablation. Analysis of the photokeratoscopic photograph showed that the distance between the central rings increased progressively after the first two ablative steps (Figure, top right). Photokeratoscopic pictures were analyzed quantitatively with the Kera-Scan Unit (Kera Corporation, Santa Clara, California) after calibration by using steel balls of known radius of curvature. The second and third rings showed statistically significant flattening of 3.09 diopters ($P < .04$) and 5.56 diopters ($P < .001$), respectively, with a 50-μm ablation, and further flattening with ablation to 100 μm. After a third 50-μm ablation (to a total depth of 150 μm), the photokeratoscopic rings disclosed a central corneal resteepening (Figure, bottom left), with corneal power exceeding that measured preoperatively. Ultrasonic pachymetry results confirmed 50-μm ablations (within 5 μm) with each ablative step.

Our objective in doing this pilot study was to determine how deep the central corneal ablation could be made before the cornea might steepen as a consequence of bulging of the central cornea. We anticipated that a central steepening would eventually occur as we ablated deeper into the stroma. Based on our findings in eye bank eyes, we have concluded that the central cornea may begin to steepen with ablations of 150 μm or greater. Our results must be interpreted with some caution because we do not know whether the same results would be obtained in a living human eye. Also, photokeratoscopy in animal and eye bank eyes is likely to be less accurate that in seeing, fixing human eyes because of difficulty aligning the eye and instrument in exactly the same manner. We can only speculate as to why we observed central steepening after 150-μm ablations compared to statistically significant flattening after 50- and 100-μm ablations. One possibility is that the structural integrity of the stromal lamellae is weakened as ablations proceed deeper into the stroma. We believe that these findings



should be considered when planning phototherapeutic applications of excimer laser surgery. Central corneal steepening might be observed after ablations of anterior stromal opacities deeper than 150 μm.

Reference

1. Stark, W. J., Gilbert, M. L., Gottsch, J. D., and Munnerlyn, C.: Optical pachymetry in the measurement of anterior corneal disease. An evaluative tool for phototherapeutic keratectomy. Arch. Ophthalmol. 108:12, 1990.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Anisocoria in the Pigmentary Dispersion Syndrome

EDITOR:

In the article, "Anisocoria in the pigmentary dispersion syndrome," by R. M. Feibel and J. C. Perlmutter (Am. J. Ophthalmol. 110:657, December 1990), the authors state, "The currently accepted hypothesis of the pathogenesis of pigmentary dispersion is that mechanical friction between anterior packets of zonules in the back of the peripheral iris cause the pigment loss in the iris." Indeed, this seems to be an eminently sensible explanation for the pattern of loss of pigment in the pigmentary dispersion syndrome. This hypothesis, however, does not appear to be adequate to explain why the pigment loss occurs in some individuals and not in others.

We[1] believe that there is probably an abnormality of the pigment epithelium of the iris itself, and histopathologic studies support this. Another possible explanation for increased iris transillumination in one eye is a greater chamber depth in the affected eye. This would be a reasonable explanation in Cases 1 and 4, in which the greater amount of transillumination occurred in the eye with the greater degree of myopia. This would not appear to account for the anisocoria.

GEORGE L. SPAETH, M.D.
Philadelphia, Pennsylvania

Reference

1. Rodrigues, M. M., Spaeth, G. L., Weinreb, S., and Sivalingam, E.: Spectrum of trabecular pigmentation in open-angle glaucoma. A clinicopathologic study. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:258, 1976.

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Atlas of Ophthalmic Surgery. By Norman S. Jaffe. Philadelphia, J. B. Lippincott, 1989. 320 pages, index, illustrated. $175

Reviewed by MARK J. MANNIS
Sacramento, California

Derived from the Greek legend depicting the giant compelled to support the heavens on his shoulders, the word "atlas" has evolved over the centuries to connote a genre of books. Volumes containing collections of maps took on the name of the gargantuan because of the picture that often appeared on the frontispiece of Atlas supporting the globe. The term has become generalized to refer to any book, often large format, of tables, plates, or illustrations on a specific subject or subjects.

The stated goal of this atlas is to provide a comprehensive visual reference, combined with an integrated text, on the important surgical subspecialties in ophthalmology. Although the text is multiauthored, the editing provides a relatively uniform treatment of the different subjects throughout the book. Proceeding on the premise that visual stimuli, by way of photography and illustration, are the most useful media for providing clarification of surgical techniques, the editor has used the maximum of excellent color photography in combination with the minimum text required to clarify the photographs and diagrams. An attempt has been made to select the surgical approaches in each subspecialty that are most universally accepted.

Of the 328 pages, the first 128 are dedicated to cataract surgery and the management of its complications. Specific subjects included are phacoemulsification, planned extracapsular extraction, lensectomy and vitrectomy, infantile cataract surgery, and a discussion of various types of posterior chamber intraocular lenses and fixation techniques. Additionally, this section includes text and photographs on the management of lens malposition, anterior chamber lenses, secondary lens implantation, posterior capsular opacification, postoperative endophthalmitis, epithelial downgrowth, abnormalities of anterior chamber depth, and lens extraction in special situations. Chapter 2 deals with the techniques in corneal transplantation. Subsequent chapters deal sequentially with surgery for glaucoma, surgery of the retina and vitreous, strabismus surgery, surgery of acquired eyelid malpositions, refractive surgery, and laser surgery of chorioretinal diseases. Surprisingly, there are no chapters on oculoplastic surgery in general, lacrimal surgery, or orbital surgery.

The great strength of this book is the spectacular photographs, especially in the chapters on cataract, strabismus, and eyelid surgery. For clarification, excellent color-coded diagrams have been included, which greatly enhance the surgical photographs. This text will have shortcomings for the reader who expects extensive verbal descriptions of the procedures or an exhaustive reference list. References included at the end of the book are not linked to textual annotation and are limited to selected papers and related texts.

This book is an atlas, however, not a surgical text. As a pictorial "how-to-do-it," it is perfect for the resident-in-training or the novice surgeon who need to be familiarized with basic surgical techniques.

Angle-Closure Glaucoma. By Stanley Hyams. Amsterdam, Kugler and Ghedini Publications, 1990. 186 pages, index. $45

Reviewed by HOWARD PERELL
Baltimore, Maryland

This monograph compiles and organizes hundreds of research articles. This collection of international articles, which span over 100 years, focuses on various aspects of angle-closure glaucoma. Twenty chapters, which vary in length from two to 17 pages, include information on classification, prevalence, mechanism, examination, causes, treatments, and prognosis of angle-closure glaucoma. Each chapter is further divided into pithy subsections that are expertly footnoted for the physician seeking indepth information. For example, in one paragraph section entitled "The Effect of an Attack on the Cornea," the five articles

referred to are not only clearly referenced but also include the author's annotations.

Except for the omission of bold chapter numbers to accompany the chapter titles, which makes chapters more difficult to locate, the work is well organized with helpful references. The quotations beginning each chapter illuminate Dr. Hyams' interest in the history of ophthalmology and his sense of humor.

In this era of laser technology, Dr. Hyams has once again focused our attention on angle-closure glaucoma, pointing out that peripheral iridotomy is not a panacea. He clearly demonstrates that the advent of medical lasers has forced us to reestablish guidelines for medical and surgical management of this condition. The author emphasizes that laser intervention is not a benign procedure and that consideration of laser intervention deserves the same scrutiny in selection of patients as did previous incisional surgical procedures.

This monograph is a well-written distillate of a large amount of previously researched material. This succinct work is important because the physician is challenged to consider the treatment of the disease in light of new pharmaceutics and interventional capabilities. The text can be placed proudly in any physician's and scholar's library, where it will be removed frequently from the bookcase and placed on the reading desk.

Visual Allusions. Pictures of Perception. By Nicholas Wade. Hove, East Sussex, England, Lawrence Erlbaum Associates Ltd., 1990. 288 pages, index, illustrated. $42.95

Reviewed by PETER THOMPSON
Montgomery, Alabama

Most of this book is devoted to an intriguing, if somewhat headache-producing, collection of the author's own graphic images. The majority of them are obsessively patterned op-art designs with mysterious hidden faces. The dazzling patterns produce sensations of shimmering movement. The author argues cogently that these effects are the result as much of the mental components of the perceptual process as they are of visual optics or the geometry of the retinal receptors.

The remaining one third of the volume is taken up with a text that is largely a restatement of the basic concepts of visual perception. Its value comes from the passages in which the author summarizes and clarifies things that have been written elsewhere.

A chapter on words and images promises valuable insights into the relationship between arbitrary letterforms and representational images. The author gets Magritte's "This is not a pipe" between his teeth and begins to ponder it in depth, ruminating on various ambiguous combinations of words and images. Then he gives us a series of images in which he has obscured some potentially identifiable face with an appropriate text, Jean-François Champollion, for example, hidden within the text of the Rosetta stone, and tells us in some detail how he made the pictures.

Some of the chapters may be tiresome, but their bibliographies are excellent and rich with annotations. The bibliography constantly reminds the reader that there are many good books on visual perception, and that this idiosyncratic and self-indulgent book is not one of them.

Clinical Tests of Vision. By Lars Frisén. New York, Raven Press, 1990. 212 pages, index, illustrated. $59

Reviewed by MICHAEL WALL
New Orleans, Louisiana

This text aims to review the clinically useful tests of sensory visual function with an "emphasis on understanding: understanding the measuring principles, understanding how the results reflect the state of the visual system, and understanding how to use the results in clinical decision making." The book brilliantly accomplishes this goal. Pathophysiologic principles are stated clearly and concisely; areas of controversy are reviewed and well referenced.

The book begins with the development of a model of the sensory visual system and explains how the model reacts when injured. Frisén emphasizes that with some visual tests we may not really know what it is we are measuring. For example, although conventional perimetry uses quantitative steps, what spe-

cifically is being measured? What do the results mean in anatomic terms?

Chapter 2, Measuring Vision, is a well-written section on the psychophysical factors involved in quantitation of vision. Frisén's use of frequency-of-seeing curves and probit analysis should make all readers rethink the way they record and interpret visual acuity measured at a Snellen chart.

Although visual acuity is covered thoroughly, contrast sensitivity is only briefly reviewed. Some authorities would disagree with the suggestion that a clinically useful application for contrast sensitivity is yet to be found.

The chapter on color vision emphasizes detecting acquired rather than congenital defects. There is little coverage of electrophysiologic testing (visual-evoked potential, electroretinography), which reflects the bias of the author (and most neuro-ophthalmologists) that these tests are seldom necessary for clinical decisions.

Much of the text deals with perimetry, which is a testimony to the author's perimetric craftsmanship. Frisén's recommendations of when to leave isopters uncompleted, when not to map the blind spot, and how to improvise strategies are admirably conceived. Visual acuity measurements are integrated into the perimetry section with a discussion of high-pass resolution perimetry. The section on comparison of manual and automatic methods is superb. The author's extensive experience with these methods is apparent.

Chapter 9 is probably the best discussion available on selection of equipment for perimetry. It integrates hardware, software, ergonomics, and cost. Test cases in the last chapter are entertaining and serve to reinforce the principles for clinical decision making.

The evolution of various visual field defects is graphically depicted in three-dimensional models of the visual field. The illustrations are clear and of high quality. The index is adequate.

The sometimes highly technical writing is interspersed with wit. This technical writing is slow reading at times, but it is necessary for the focus on understanding basic principles and their application. The book accomplishes its aims by being on the level of both the newcomer to visual testing and the visual scientist. I highly recommend "Clinical Tests of Vision" to all readers with a serious interest in measurement of the sensory visual system and its clinical application.

Retinal Nerve Fiber Layer Photography. By Louis W. Roloff. Thorofare, Slack, 1990. 174 pages, illustrated. $90

Reviewed by NANCY NEWMAN
Mill Valley, California

This atlas is short and nicely formatted, with large photographs of the posterior pole printed on good quality paper. There are only a few pages of text, but the photographs are fully captioned.

The text is designed to help the physician and the retinal photographer to recognize nerve fiber layer changes. The emphasis is on normal variants and glaucomatous damage. Some photographs are less than optimal examples deliberately chosen to portray the "real world" of nerve fiber layer photography. The author is to be complimented for his courage in presenting the unretouched photographs. Unfortunately, this often means that the optic disk details, so helpful in the interpretation of nerve fiber layer changes, are lost.

The author outlines his technique for "monochromatic" nerve fiber layer photography; however, there is no mention of the many other techniques that have been applied to nerve fiber layer imagery: other photographic methods; enhancement techniques, such as subtraction and polarization; computerized image analysis; and densitometric studies; which in the future will permit quantification and give greater power to this diagnostic technique.

I have several quibbles. Strictly speaking, the technique is not monochromatic; narrow bands of transmitted light are used. Customary usage suggests that the terms "slit defect" and "rake defect" both refer to long narrow areas of nerve fiber atrophy, but the author seems to equate rake defects with pseudodefects. There are only a few examples in the atlas of neuro-ophthalmic nerve fiber layer alterations and no examples of the changes seen in retinal dystrophies. From the clinician's standpoint, many patients with these diseases have visual loss or, like the patient with glaucoma, have previously unsuspected visual field defects. The differential diagnosis of the changes in the nerve fiber layer are often critical for proper patient treatment.

This is a valuable book, as far as it goes. Perhaps the next edition will discuss alternative techniques, other developments in the field,

other optic neuropathies, and recent advances in technology and cite the sources of this information.

Lens Implant Power Calculation, ed. 3. By John A. Retzlaff, Donald R. Sanders, and Manus Kraff. Thorofare, Slack, 1990. 58 pages, illustrated. $20

Reviewed by H. E. KOLDER
Iowa City, Iowa

This manual is a somewhat dry exposition of that mixture of biometry, applied mathematics, and art that the ophthalmologist uses to estimate the ideal power of an implant lens. The historical review in the opening chapter makes it evident that theoretical and empirical formulas can indeed satisfactorily predict the implant lens power needed in an eye of normal axial length (22.5 to 24.0 mm). Refinements of the formula become important in eyes that are unusually short or unusually long. The SRK II and SRK/T (theoretical) formulas extend the range of usefulness of the original SRK formula by incorporating nonlinear terms into the calculations.

Useful chapters are included on biometric, ocular, and manufacturing factors influencing the calculation. Look-up tables provide primary data (for example, the center thickness of various intraocular lenses), from which small corrections can be derived. A critical assessment is given of the A constant, the estimate of anterior chamber depth, and the surgeon's personal fudge factor. When an abnormal measurement is encountered, prompts for trouble shooting are offered, which enable the surgeon to check systematically for sources of error. The appendix is helpful, not only because it juxtaposes the various formulae, but also because the terminology is defined and then used in a consistent manner. The list of references includes 227 articles not easily accessed. Approximately half of all pages in the manual are reserved for reprinting the authors' germane original articles.

Every time an intraocular lens is implanted, the lens power must be selected and all the while a multitude of perplexing factors buzz threateningly around the ophthalmologist's head. This manual cuts quickly and thoroughly through these difficulties. I recommend it highly.

Laser Surgery of the Posterior Segment. By Steven M. Bloom and Alexander J. Brucker. Philadelphia, J. B. Lippincott, 1990. 341 pages, index, illustrated. $69.95

Reviewed by H. STANLEY THOMPSON
Iowa City, Iowa

This book, although physically pleasing, is not a teaching book; it is a reference book. The entire text has been done in outline form, and more care has been given to the classification of knowledge than to its delivery. I find this format decidedly unfriendly. I opened the book just to browse around, but there was no human voice there in the words to explain things to me. Each page was a dry list of topics, subclasses, and subcategories, none of which made any sense to me, at least not until I had wrestled the entire framework of the chapter to the ground.

Laser surgery of the retina must be one of the authors' favorite subjects at the moment, yet they do not want to take the trouble to show me around and tell me all about it. It seems impolite, somehow, and I find myself resenting it. I will not be the only would-be reader who feels the chill of rejection and closes the book.

This is not to say that the book is without value. It is well suited for the retinal specialist looking for a modern review of the literature. Retinal fellows looking for a way to subdivide systematically this part of their subspecialty may want to buy it, for example, to organize a reprint collection, but the beginning resident and the practicing ophthalmologist will not like it.

If the next edition were to be offered in a machine-readable outline format, it might be possible for the purchaser not only to categorize this subspecialty for retrieval purposes but also to add new references as they come along so that the file will stay up-to-date.

Style. Toward Clarity and Grace. By Joseph M. Williams. Chicago, University of Chicago Press, 1990. 193 pages, index. $17.95

Reviewed by FRANK W. NEWELL
Chicago, Illinois

Williams is professor in the departments of English language and literature, and linguistics at the University of Chicago. He is the author of a standard textbook on writing style that has appeared in three editions. This volume is designed to be used outside of the classroom. It seeks to explain how writers can improve the style and structure of their reports. There are many suggestions and a happy avoidance of rules of English usage: " . . . all . . . must understand three things about complex writing: it may precisely reflect complex ideas; it may gratuitously complicate complex ideas; it may gratuitously complicate simple ideas."

Williams attributes current poor writing of English to the Norman conquest of 1066, which led to a vocabulary qualitatively different from the Anglo-Saxon, and to Renaissance scholars speaking Norman French and translating Greek and Latin texts into English. This provided the basis for a varied and rich vocabulary but brought with it the danger of expressing action with abstract romance nouns rather than specific verbs. An example follows: "The dean's proposal would replace the faculty . . . "; "The dean proposed to replace the faculty . . . ."

He provides a number of principles: "(1) the subjects of the sentences name the cast of characters, and (2) the verbs that go with those subjects name the crucial actions those characters are part of." Some examples follow: "There has been an affirmative decision for program termination." "The director decided to terminate the program." "The police conducted an investigation into the matter." "The police investigated the matter."

Put at the beginning of the sentence the ideas already mentioned. Put at the end of the sentence the newest ideas. Not: "A black hole is created by the collapse of a dead star into a point perhaps no larger than a marble." Instead: "The collapse of a dead star into a point perhaps no larger than a marble creates a black hole."

This volume is most appropriate for each of us who have rewritten and rewritten a paper and then had it returned with the suggestion that its style was turgid.

The last paragraph of the volume quotes Alfred North Whitehead:

> Finally, there should grow the most austere of all mental qualities; I mean the sense for style. It is an aesthetic sense, based on admiration for the direct attainment of a foreseen end, simply and without waste. Style in art, style in literature, style in science, style in logic, style in practical execution have fundamentally the same aesthetic qualities, namely, attainment and restraint . . . . Style, in its finest sense, is the last acquirement of the educated mind; it is also the most useful. It pervades the whole being. The administrator with a sense for style hates waste; the engineer with a sense for style economizes his material; the artisan with a sense for style prefers good work. Style is the ultimate morality of the mind.

Books Received

Advances in Cataract Surgery. Edited by Glen C. Cangelosi. Thorofare, Slack, 1990. 239 pages, index, illustrated. $80

These are the proceedings of the 39th Annual Symposium of the New Orleans Academy of Ophthalmology held in March 1990.

Complications of Glaucoma Therapy. By Mark B. Sherwood and George L. Spaeth. Thorofare, Slack, 1990. 390 pages, index, illustrated. $90

Eighteen authors contribute 35 papers on things that can go wrong when patients with glaucoma are treated with drugs, lasers, or surgery.

Current Concepts of Multifocal Intraocular Lenses. Edited by Andrew Maxwell and Lee T. Nordan. Thorofare, Slack, 1990. 239 pages, index, illustrated. $80

Cataract surgeons continue to make use of newer and still newer technical advances. If you want to keep up with what is happening, read about it in this series of 19 papers by 31 contributors to a symposium held in April 1990.

Laser. Its Clinical Uses in Eye Diseases, ed. 2. By Ian J. Constable and Arthur Siew Ming Lim. New York, Churchill Livingstone Inc., 1990. 207 pages, index, illustrated. $85

An atlas of beautifully printed fundus photographs with minimal text. Four new chapters have been added to this edition.

Les Strabismes. De l'analyse clinique à la synthèse chirurgicale, ed. 2. By Annette Spielmann. Paris, Masson, 1990. 292 pages, index, illustrated. (No price given)

Dr. Spielmann is an ophthalmologist in Nancy, France, and this is the second edition of her thorough textbook. Every American ophthalmologist with an interest in strabismus will learn something from this text, if only from the diagrams showing fresh explanations of concepts and slightly different ways of examining children.

The Molecular Biology of the Retina. Edited by Debora B. Farber and Gerald J. Chader. New York, John Wiley & Sons, 1990. 245 pages, index, illustrated. $80

Nine papers are printed in typescript form in this volume. The papers were presented at a symposium held in San Francisco in September 1988 as part of the International Society of Eye Research.

Ophthalmic Echography. Ophthalmic Technical Skills Series. By Cynthia J. Kendall. Thorofare, Slack, 1990. 179 pages, index, illustrated. $37

This is a practical review of ophthalmic ultrasound addressed to the ophthalmic technician.

Retinal and Choroidal Manifestations of Systemic Disease. By Lawrence J. Singerman and Lee M. Jampol. Baltimore, Williams & Wilkins, 1990. 298 pages, index, illustrated. $39.50

A well-made book covering several important topics, including AIDS, carotid artery disease, hypertension, and pregnancy. These ten review papers were presented at a symposium sponsored by the Macula Society at the American Academy of Ophthalmology in October 1988.

Small-Incision Cataract Surgery. Edited by James P. Gills and Donald R. Sanders. Thorofare, Slack, 1990. 271 pages, index, illustrated. $100.

This volume, with 20 papers by 21 contributors, records some of the recent progress in cataract surgery, emphasizing the advantages of small incisions and foldable lenses. These editors seem to be especially sensitive to the beauty of a smoothly functioning system and have taken the trouble to fill their book with high-quality color photographs and crisp diagrams.

Textbook of Advanced Phacoemulsification Techniques. Edited by Paul S. Koch and James A. Davison. Thorofare, Slack, 1990. 414 pages, index, illustrated. $100

A book of essays on various aspects of cataract surgery, written in a comfortable style and profusely illustrated.

Visual Fields. Examination and Interpretation. Edited by Thomas J. Walsh. San Francisco, American Academy of Ophthalmology, 1990. 248 pages, index, illustrated. $55

Dr. Walsh has been assisted in this endeavor by his Yale colleagues Joseph Caprioli and James Abrahams, by Thomas Hedges from Philadelphia, and by neuro-ophthalmologists Jonathan Wirtschafter and Brian Younge from Minnesota.

This text was apparently conceived as an update of a venerable Academy manual by Wilbur Rucker. Even those of us who remember Rucker's version will have trouble making the connection because the computer revolution has put color diagrams on almost every page,

placed blue arrows on the magnetic resonance images, and scattered gray-scale visual fields from automated perimeters throughout the book.

Every resident in ophthalmology should be grateful to the Academy for preparing this manual. It is exactly the kind of supplemental information needed to fill in the corners of the training program. Even if you do not read Dr. Walsh's preface, the main point comes across loud and clear: visual fields are an important part of every ophthalmologist's examination and should not be thought of as an occasional special study done by someone else.

The Book List

Age-Related Cataract. By Richard W. Young. New York, Oxford University Press, 1990. 290 pages, index. $55

Eyelid Surgery. By J. Earl Rathbun. Boston, Little, Brown and Company, 1990. 290 pages, index, illustrated. $150

Graves' Ophthalmopathy. Edited by Jack R. Wall and Jacques How. St. Louis, Mosby-Year Book, 1990. 196 pages, index, illustrated. $49.95

Meetings

Ocular Microbiology and Immunology Group—24th Annual Meeting

The 24th annual meeting of the Ocular Microbiology and Immunology Group was held Oct. 27, 1990, in Atlanta.

J. B. Robin, K. A. Kalinski, and M. Griffith evaluated the use of peroxidase-conjugated lectins in the visualization of *Candida albicans* and *Aspergillus* species by using simple light microscopy. Both organisms were readily and consistently visualized. These preliminary results indicate that peroxidase-conjugated lectins may provide an alternative to conjugated lectins for the visualization of microorganisms.

D. C. Gritz, S. Kwitko, M. D. Trousdale, V. H. Gonzalez, and P. J. McDonnell studied the recurrence of keratitis caused by *Pseudomonas aeruginosa* or *Streptococcus pneumoniae* in rabbits treated with specific antibiotic therapy and corticosteroids. Infection with *P. aeruginosa* recurred on cessation of antibiotic therapy but streptococcal infection did not recur.

J. N. N. Feder, J. E. Egbert, P. A. Raposa, J. W. Chandler, and T. D. France described the successful resolution of *Pseudomonas mesophilica* keratitis after treatment with topical piperacillin.

A. Perry, R. A. Copeland, Jr., and R. P. Mason described the course and treatment of *P. aeruginosa* conjunctival abscesses in a diabetic patient.

M. G. Reynolds and E. Alfonso described a series of 28 patients with infectious scleritis. Involvement of the adjacent cornea was associated with a poor prognosis.

D. J. Harris, Jr., described a case of *Branhamella* species colonization of exposed nylon sutures.

R. P. Kowalski, L. Karenchak, and M. L. Roat investigated the in vitro susceptibility of ocular streptococcal isolates to polymyxin B and trimethoprim, the active agents of Polytrim. They found a variable resistance among the strains they tested.

D. N. Skorich reported a case of bilateral *Kingella kingae* corneal ulceration that occurred in a 50-year-old alcoholic man.

S. Feldman, N. Socci, and B. Frueh described two cases of atypical mycobacterial scleroker-atitis that occurred after penetrating keratoplasty.

T. B. Cavanaugh and J. D. Gottsch reported three cases of late-onset infectious keratitis that developed after the use of glue and despite prophylactic antibiotic therapy. Masking of the underlying infection and the development of resistant organisms should be considered when using this mode of therapy.

R. G. Fante and R. W. Snyder found that subconjunctival injection of tobramycin was effective in producing high scleral, corneal, and aqueous levels of the drug early in the course of treatment.

R. Haimovici, E. Alfonso, K. Wilhelmus, T. O'Brien, and R. Abshire reported on a trial of ciprofloxacin in the treatment of presumed microbial keratitis. For a broad spectrum of organisms, they found the agent to be effective when administered topically as a 3% solution.

J. D. Bulloch, M. S. Jedrzynski, T. W.

Maguire, and B. L. Elder described the development of anaerobic orbital cellulitis in five patients and discussed an animal model of the disease.

M. G. Speaker, F. A. Milch, B. N. Kreisworth, and A. K. Shah discussed the role of external ocular bacterial flora in the pathogenesis of acute postoperative endophthalmitis in their series. The patient was the source of the organism in a majority of cases in their series.

D. M. O'Day, R. Wolff, S. Head, R. Robinson, and T. Williams studied the reliability of sampling of the vitreous as a measure of the extent of infection in experimental endophthalmitis. Culture, positivity, and isolate recovery rates from vitreous samples did not correlate with isolate recovery rates from whole vitreous or whole eyes.

A. M. Mansour, E. Ferguson, H. L. Li, and H. Lucia described two patients with severe bacterial endophthalmitis who were treated by subtotal replacement of the vitreous by perfluoropropane gas.

R. N. Sjaarda, D. W. Parke III, and M. D. Osato in an in vitro study failed to find that perfluoropropane and sulfur hexafluoride had any inherent antimicrobial properties.

T. John and A. G. Noble described the occurrence of *Pseudomonas* corneal ulceration in three patients who underwent mechanical ventilation in the intensive care unit.

A. E. Schwartz, A. Sugar, A. K. Vine, and J. R. Wolter described a case of persistent *Candida parapsilosis* endophthalmitis, which responded to treatment with fluconazole.

T. W. Maguire, J. D. Bulloch, L. Elder, and J. W. Funkhouser, in a comparison of endophthalmitis caused by *Aspergillus fumigatus* and *Pseudomonas boydii* found the infections to be indistinguishable in immunocompetent and immunosuppressed exogenously infected rabbits.

M. Busin, I. Bechrakis-Böker, and T. Böker described a combined medical and surgical approach to a fungal corneal abscess.

C. M. Parrish and B. Crowley described a case of oculoglandular syndrome secondary to *Tularemia* species.

D. J. Doughman, D. R. Hardten, E. J. Holland, and T. W. Gothard described two patients with *Chlamydia trachomatis* conjunctivitis who developed a persistent superficial keratitis. The lesions resolved promptly after treatment with topical corticosteroids.

N. Kerr and G. Stern described the occurrence of bacterial keratitis in patients with vernal keratoconjunctivitis. In three of four patients, the infections were polymicrobial and responded to appropriate antibiotic therapy.

K. A. Buzard and M. O'Hanlan described the use of low-dose methotrexate in the treatment of external ocular inflammatory disease.

S. D. Trocme, G. B. Bartley, G. J. Gleich, and K. M. Leiferman demonstrated the presence of extracellular eosinophilic major basic protein and extracellular neutrophil elastase in the tissues of two eyes of patients with Wegener's granulomatosis. They postulated an active role of both eosinophils and neutrophils in the development of corneoscleral lesions in patients with this disease.

S. Butrus and L. Schwartz found that MC_{TC} mast cells predominate and are increased in giant papillary conjunctivitis. There was also an increase in tryptase, a specific mast cell marker, in these patients.

S. H. Soukiasin, C. S. Foster, and M. Raizman demonstrated the presence of antineutrophil cytoplasmic antibodies in six patients with scleritis and peripheral ulcerative keratitis. They believe that scleral biopsy, by demonstrating granulomatous reaction with or without vasculitis, is helpful in making the appropriate diagnosis.

L. P. Fong and C. S. Foster studied 25 patients with necrotizing scleritis and five patients with chronic nonnecrotizing scleritis with the aid of scleral and conjunctival biopsies. These biopsies showed that vasculitis was a common finding, immune complex deposition was occurring in vessel walls, and there was a significant increase over normal controls in the number of T-helper lymphocytes, T lymphocytes, macrophages, and expression of HLA-DR determinants.

R. Belfort, Jr., W. deSmet, R. Rubin, J. Balkissoon, R. Nussenblatt, and S. A. Rosenberg discussed the development of scleritis and sclerouveitis in three patients receiving recombinant human macrophage colony stimulating factor for the treatment of advanced cancer. The findings resolved when the agent was stopped.

A. Fox, K. Fox, V. Pakalnis, and W. Kosdnosky studied polypeptide profiles of normal aqueous and aqueous from animals injected with muramyl dipeptide, a monomer of cell walls of gram-positive and gram-negative bacteria that causes a severe, short-term breakdown of the blood aqueous barrier. Their findings suggest that changes in the protein composition in ocular inflammation result primarily from the influx of serum.

E. Arocker-Mettinger, T. Asenbauer, V. Huber-Spitzy, and G. Grabner measured levels of interleukin 2-receptor (IL-2R) in patients with uveitis. Interleukin 2-receptor serum levels were increased in patients with Fuchs' heterochromic cyclitis and in children with juvenile rheumatoid arthritis–related chronic iridocyclitis.

K. J. Johns described a patient with X-linked hypogammaglobulinemia who developed intensive cellular infiltration of the vitreous bilaterally. The infiltrate was unresponsive to all attempts at therapy.

C. M. Kaslow and P. Gollin examined the rabbit pineal gland for immunoreactive S-antigen by using a panel of monoclonal antibodies. The monoclonal antibodies failed to react with rabbit pineal gland as they reacted with guinea pig or rat pineal, supporting the hypothesis that the autoimmune response in the pineal gland modulates uveitis induced by S-antigen sensitization.

N. P. Barney, M. S. Blumenkranz, and C. S. Foster described the presence of cotton-wool spots and T-cell abnormalities in a 72-year-old woman with temporal arteritis.

E. H. Sato, H. Ariga, A. C. Vendramini, and D. A. Sullivan used a mouse model to investigate the possible role of androgen therapy for Sjögren's syndrome. They found that testosterone therapy suppresses autoimmune disease in the lacrimal gland in the mouse.

K. Tsubota, I. Saito, S. Nishimura, J. Yodoi, and I. Moro detected anti–T lymphocyte–derived factor (ADF) in ductal epithelial cells and some large lymphoid cells in salivary gland and lacrimal gland biopsy specimens, suggesting that ADF from Epstein-Barr virus–infected cells could be involved in interleukin 2-receptor induction and the progression of lymphocyte activation of Sjögren's syndrome.

I. R. Schwab described the use of eicosapentaenoic acid derived from cold-water fish in the treatment of patients with meibomian gland dysfunction. Five of seven patients had measurable objective and subjective improvement in their signs and symptoms.

M. S. Osato, M. Pyron, K. R. Wilhelmus, R. F. Font, and D. B. Jones assessed the pathogenesis of *Acanthamoeba* keratitis in vitro by comparing the invasiveness of three species of amebae in an epithelial sheet assay as well as the capacity to penetrate human corneal stroma. All three species were able to invade the corneal epithelium but stromal invasion differed among the strains.

E. H. Holland, I. H. Alul, R. J. Epstein, and D. M. Meisler described the development of anterior stromal corneal infiltrates late in the course of *Acanthamoeba* keratitis. They postulated that an immunologic mechanism may be responsible.

G. Rosenwasser, D. Cunningham, and W. Greene presented a videotape of onchocerciasis in the human eye.

Y. J. Gordon, E. Romanowski, T. Araullo-Crus, L. Seaberg, S. Erzurum, R. Tolman, and E. de Clercq evaluated in vitro the new antivirals (s)-9-(3-hydroxy-2-phosphonylmethoxypropyl) (HPMPA) and 2'-nor-cyclic GMP against a series of adenoviral serotypes. Using plaque reduction and cyclopathogenicity assays, they found all three to have significant activity against adenovirus types 1, 5, 8, and 19.

G. Stevens, J. Harmon, R. Rajpal, and H. Ballitch reported a case of herpes simplex keratitis that failed to respond to vidarabine, trifluridine, and débridement but improved rapidly with acyclovir treatment.

J. Colin, F. Mallet, and M. C. Richard described the use of collagen shields soaked in 1% trifluorothymidine in the treatment of dendritic keratitis.

M. J. Mannis, R. Plotnik, I. R. Schwab, and D. Newton described the development of herpes simplex keratitis in three patients, three to 11 months after keratoplasty.

D. deFreitas, D. Pavan-Langston, L. D. Kelly, B. L. Rong, E. C. Dunkel, E. H. Sato, and K. R. Kenyon described the development of varicella-zoster keratitis in two children after the onset of typical chickenpox rash.

K. S. Keefe and J. E. Sutphin described the clinical course of unilateral zoster keratitis and uveitis in a patient with AIDS. Ipsilateral cerebral infarction occurred despite prolonged systemic antiviral therapy.

W. H. Greene, G. O. Rosenwasser, and B. J. Howard described the occurrence of infection with herpes simplex virus types 1 and 2 in a patient with AIDS.

D. Laby, J. Orenstein, S. Butrus, A. Hidayat, and P. Whitmore described a patient with AIDS who developed intraocular infections with toxoplasmosis, cytomegalovirus, and herpes simplex.

R. R. Johnson, G. G. Cooper, and R. S. Weinberg described the development of *Pasteurella multocida* keratitis in an 85-year-old woman with multiple myeloma.

DENIS M. O'DAY

Obituary

J. GRAHAM DOBBIE

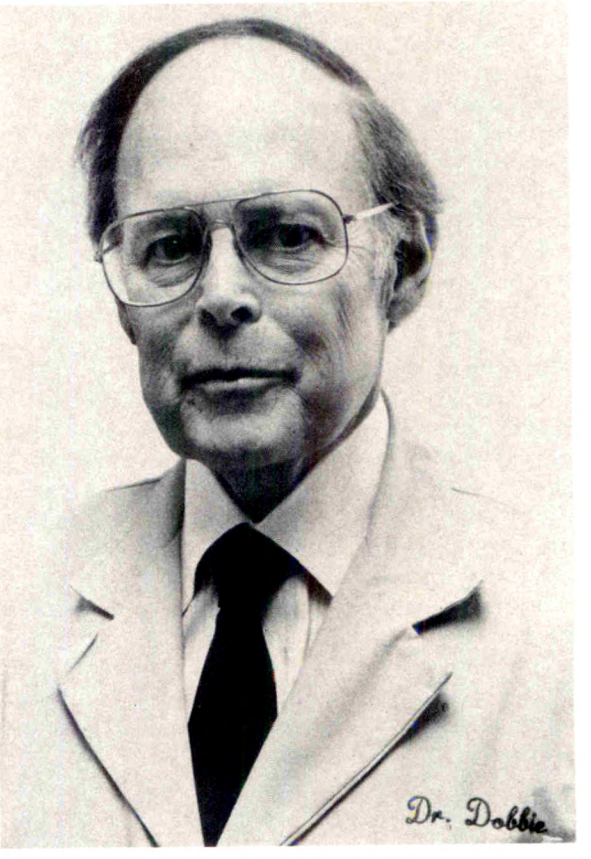
1926–1990

J. Graham Dobbie, professor of ophthalmology and founder of the retina service at Northwestern University, died of cancer at his home in Chicago on Dec. 1, 1990.

Graham's career as a physician and teacher spanned nearly 30 years, beginning on his return to Chicago in 1961 as the area's first retinal surgeon. It was a time when indirect ophthalmoscopy and scleral buckling were virtually unknown in many areas throughout the Midwest, which prompted Graham to recall years later that his early lectures on the direct ophthalmoscope and peripheral retina were often met with respect but minimal enthusiasm. He traveled among several Chicago institutions in those first years, founding and directing retina services at Cook County and Hines Veteran Administration hospitals, and in 1963, the retina department and laboratory at Northwestern University where he served as director until 1985.

Graham was born on April 28, 1926, in Oak Park, Illinois. After high school, he enlisted in the United States Navy and became a demolition expert. He used to joke that it was this early training in handling explosives that contributed later to his dexterity and good judgment in the operating room. He graduated from Northern Illinois University in 1950 and received his medical degree in 1955 from Marquette University where he was an honors graduate and a member of Alpha Omega Alpha. He served his internship and residency at Cook County Hospital, where he met and then married his wife, Rosemarie. The following year he received his master of science degree in physiology at Loyola University. This interest in physiology took him to London in 1958, where as a special National Institutes of Health fellow he studied physiologic mechanisms in glaucoma. Personal contacts that year with many British and European research ophthalmologists developed into endearing friendships that remained very special to him for the rest of his life.

In 1959, Graham began a retinal fellowship with Charles Schepens at the Massachusetts Eye and Ear Infirmary and the Retina Foundation. Although he loved Boston and considered staying, he wanted most of all to start his own practice and establish a retinal center in Chicago. He joined the teaching staff at Northwestern University in 1961 as clinical assistant, the first subspecialist in the department, and in 1984 was appointed professor of ophthalmology.



J. Graham Dobbie

1926–1990

Graham was a charter member of the Retina Society and president in 1986 and 1987. He was elected to the American Ophthalmological Society in 1980 and was a member of the Club Jules Gonin, Oxford Ophthalmological Congress, American Academy of Ophthalmology, and the Eye Study Club. He devoted many years to the Chicago Ophthalmological Society and, as its president in 1974, guided the society through a difficult period of emerging concern over ethical standards and proper conduct related to physicians and advertising.

Graham published over 50 articles on diseases and surgery of the retina and was a frequent visiting professor and participant and moderator at numerous meetings and seminars. He was especially interested in intraocular fluid dynamics and wrote his American Ophthalmological Society thesis on circulatory changes associated with retinal detachment, a project he continued to study until a few weeks before his death.

Onchocerciasis was another of Graham's special interests. With Maurice Langham, his friend and colleague for many years, he traveled repeatedly to Africa to examine and treat patients with river blindness.

Graham was an elegant man, and his patients were devoted to him as he was to them. He is survived by his daughter Pamela, his son James, and his cousin Robert.

CARL FETKENHOUR

ABSTRACT DEPARTMENT

Edited by Michael A. Kass, M.D.

What is known about the prevention of congenital toxoplasmosis? Jeannel, D.*, Costagliola, D., Niel, G., Hubert, B., and Danis, M.: Lancet 336:359, 1990.

CONGENITAL TOXOPLASMOSIS, SCREENING

A national program to prevent congenital toxoplasmosis has been functioning in France since 1976. The program includes mandatory serologic screening of all pregnant women. Seronegative women are followed up with monthly serologic tests for toxoplasmosis. Women in whom acute infection is diagnosed in pregnancy are treated with 1 g of spiramycin three times daily. The authors questioned whether this program has been effective in reducing the incidence of fetal toxoplasmosis. The costs of the screening and treatment programs are high. Moreover, the efficacy of spiramycin in preventing contamination of the fetus, or in reducing the extent of the infection, has never been evaluated in a randomized, placebo-controlled, clinical trial. The authors question whether a program of health education aimed at pregnant women might be as effective in reducing the incidence of toxoplasmosis. Finally, the authors state that now it is impossible to conduct a clinical trial of spiramycin treatment in France. They recommend that this trial be conducted in another country.—Michael A. Kass

*Department of Medical Statistics, Gustave Roussy Institute, rue Camille Desmoulins, 94805 Villejuif CEDEX, France.

Extracorporeal photopheresis in the treatment of AIDS-related complex. A pilot study. Bisaccia, E.*, Berger, C., and Klainer, A. S.: Ann. Intern. Med. 113:270, 1990.

AIDS-RELATED COMPLEX, EXTRACORPOREAL PHOTOPHERESIS

Five patients with AIDS-related complex underwent extracorporeal photopheresis. The patients were given an oral dose of the photosensitizer, 8-methoxypsoralen. Two hours later, after absorption and distribution of the drug, blood was withdrawn, and the patients' cells were irradiated in an extracorporeal photopheresis device. After exposure to ultraviolet A, the cells were then reinfused. The treatment was administered on two successive days once a month. The therapy produced persistent disappearance of lymphadenopathy in all patients. The cultures in two patients became negative for HIV-1. The results of skin tests evaluating delayed hypersensitivity improved. The absolute CD4 cell counts increased in two patients. There was also improvement in the subjective indices of the quality of life. This preliminary trial suggests that extracorporeal photopheresis therapy may be beneficial in patients with AIDS and AIDS-related complex.—Michael A. Kass

*Photopheresis Unit, Morristown Memorial Hospital, 100 Madison Ave., Morristown, NJ 07962-1956.

European stroke prevention study. ESPS Group*: Stroke 21:1122, 1990.

STROKE, TRANSIENT ISCHEMIC ATTACKS, ASPIRIN, DIPYRIDAMOLE

There has been considerable controversy concerning whether aspirin alone or combined with dipyridamole is effective in preventing cerebrovascular disorders. In this study, 2,500 patients who had previous cerebrovascular disorders (transient ischemic attacks, reversible ischemic neurologic deficits, or completed strokes) were randomly assigned to either placebo or a capsule containing 330 mg of aspirin and 75 mg of dipyridamole administered three times daily. Treatment was associated with a 33.5% reduction ($P < .0001$) in the incidence of deaths from all causes or strokes by an intention-to-treat analysis and a 36.5% reduction ($P < .001$) by explanatory analysis. The treatment effect appeared to be similar in men and women. The effect of treatment was also similar regardless of the patient's age, nature of qualifying cerebrovascular event, site of the responsible lesion, and diastolic blood pressure. This study demonstrates the efficacy of combined treatment with aspirin and dipyridamole. The

study does not address the questions of the proper dose of aspirin and whether either drug alone is superior or equal to the combination.—Michael A. Kass

*A. Lowenthal, M.D., Jan Van Rijswijcklaan 106, B-2018, Antwerpen, Belgium.

Mutations within the rhodopsin gene in patients with autosomal dominant retinitis pigmentosa. Dryja, T. P.*, McGee, T. L., Hahn, L. B., Cowley, G. S., Olsson, J. E., Reichel, E., Sandberg, M. A., and Berson, E. L.*: N. Engl. J. Med. 323:1302, 1990.

AUTOSOMAL DOMINANT RETINITIS PIGMENTOSA, RHODOPSIN GENE MUTATIONS

Retinitis pigmentosa is genetically heterogeneous, being transmitted as an autosomal dominant trait in some families, an autosomal recessive trait in other families, and an X-linked trait in still others. A restriction-fragment-length polymorphism from chromosome 3q was found to be linked tightly to the disease trait in one large family with autosomal dominant retinitis pigmentosa. Since the gene encoding rhodopsin is on the same arm of the chromosome, an intensive search was made for mutations of the rhodopsin gene in a group of unrelated patients with autosomal dominant retinitis pigmentosa. Three mutations in the human rhodopsin gene were found in affected members of some families with autosomal dominant retinitis pigmentosa. Two mutations were C-to-T transitions involving separate nucleotides of codon 347; the third was a C-to-G transversion in codon 58. Each mutation corresponded to a change in one amino acid residue in the rhodopsin molecule. These mutations were not found in 106 unrelated normal subjects who served as controls. When the incidence of these three mutations was added to that of a previously reported mutation involving codon 23, 27 of 150 (18%) unrelated patients with autosomal dominant retinitis pigmentosa were found to carry one of these four defects in the rhodopsin gene. It is possible that patients with the mutation involving codon 23 descend from a single ancestor. Thus in some patients with autosomal dominant retinitis pigmentosa, the disease is caused by one of a variety of mutations of the rhodopsin gene.—Michael A. Kass

*Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

A mouse model of the aniridia-Wilms tumor deletion syndrome. Glaser, T.*, Lane, J., and Housman, D.: Science 250:823, 1990.

ANIRIDIA, WILMS TUMOR, ANIMAL MODEL

Deletion of chromosome 11p13 in humans produces the WAGR syndrome, consisting of aniridia (an absence or malformation of the iris), Wilms tumor (nephroblastoma), genitourinary malformations, and mental retardation. An interspecies backcross between *Mus musculus/domesticus* and *Mus spretus* was made in order to map the homologous chromosomal region in the mouse genome and to define an animal model of this syndrome. Nine evolutionarily conserved DNA clones from proximal human 11p were localized on mouse chromosome 2 near Small-eyes (Sey), a semidominant mutation that is phenotypically similar to aniridia. Analysis of Dickie's Small-eye (Sey^{Dey}), a poorly viable allele that has pleiotropic effects, revealed the deletion of three clones, f3, f8, and k13, which encompass the aniridia (AN2) and Wilms tumor susceptibility genes in man. Unlike their human counterparts, $Sey^{Dey}/+$ mice do not develop nephroblastomas. These findings suggest that the Small-eye defect is genetically equivalent to human aniridia, but that loss of the murine homolog of the Wilms tumor gene is not sufficient for tumor initiation. A comparison among Sey alleles suggests that the AN2 gene product is required for induction of the lens and nasal placodes.—Authors' abstract

*Center for Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139.

A longitudinal study of children with a family history of strabismus. Factors determining the incidence of strabismus. Aurell, E., and Norrsell, K.*: Br. J. Ophthalmol. 74:589, 1990.

STRABISMUS, ESOTROPIA, HYPERMETROPIA

A longitudinal study of ocular refraction, deviation, and fixation was performed in children with a family history of strabismus. The children were examined at regular intervals between 3 months and 4 years of age. Six of 34 children (17.6%) developed constant or intermittent esotropia. In every patient except one, strabismus was first noted between 18 and 30

months of age. All children with esotropia had 4 or more diopters of hypermetropia at 6 months of age, and their hypermetropia remained almost unchanged through the follow-up period. Seven additional children had 4 diopters or more of hypermetropia at 6 months of age, but they did not develop a squint. In contrast to the children who developed squints, the hypermetropia in the children who did not develop squints diminished during the follow-up period. The process of emmetropization was most pronounced during the first two years of life.—Michael A. Kass

*University Eye Clinic, Sahlgren's Hospital, S 413 45, Göteborg, Sweden.

Biometry of the crystalline lens in early-onset diabetes. Sparrow, J. M.*, Bron, A. J., Phelps Brown, N. A., and Neil, H. A. W.: Br. J. Ophthalmol. 74:654, 1990.

DIABETES MELLITUS, LENS CHANGES

Lenticular biometry on non-cataractous lenses has been studied by means of Scheimpflug photography and digital image analysis in 153 patients with early-onset insulin-dependent diabetes and 153 non-diabetic controls. Anteroposterior axial lens thickness, cortical thickness, nuclear thickness, anterior and posterior lenticular curvatures, and anterior chamber depth were assessed. Highly significant differences between the lenses of the diabetic subjects and non-diabetic controls were found. After the effect of age had been accounted for within the diabetic subgroup, diabetic duration was found to be a highly significant determinant of lens dimensions, such that age-related dimensional changes for various biometric parameters were accelerated by between 52% and 121% after the onset of diabetes. Because the diabetic duration of the early-onset diabetic subjects studied in this work was accurately known, this report is the first in which a precise assessment of the effect of "true" diabetic duration on lens biometry has been possible.—Authors' abstract

*Department of Ophthalmology, University of Leicester, Leicester Royal Infirmary, Leicester LEI 5WW, Great Britain.

Sports-related ocular trauma. Larrison, W. I.*, Hersh, P. S., Kunzweiler, T., and Shingleton, B. J.: Ophthalmology 97:1265, 1990.

SPORTS-RELATED OCULAR INJURIES, PROTECTIVE EYE WEAR

Over a one-year period, 202 patients with sports-related ocular injuries were examined at the Massachusetts Eye and Ear Infirmary. Most of the patients examined (81%) were male, and the mean age for all patients was 23.3 years. Projectile rather than blunt trauma caused most injuries. Of the 202 patients examined, 28 (13.8%) required hospitalization and 11 (5.6%) required intraocular surgery. Twenty-six patients (12.8%) sustained permanent ocular sequelae, including seven (3.5%) who had permanent visual loss. Most ocular injuries occurred during basketball, baseball, and racquetball games. Only 5% of the patients stated that they had used protective eye wear. Despite the injury, only 31% of the patients used protective eye wear in subsequent sports activities. It is clear that sports trauma is a significant cause of ocular morbidity and that few individuals use protective eye wear.—Michael A. Kass

*46 Prince St., Ste. 402A, New Haven, CT 06519.

Prevalence of angioid streaks and other ocular complications of Paget's disease of bone. Dabbs, T. R.*, and Skjodt, K.: Br. J. Ophthalmol. 74:579, 1990.

PAGET'S DISEASE, ANGIOID STREAKS

Many reports have linked Paget's disease with angioid streaks and subretinal neovascularization. Seventy randomly selected patients with Paget's disease were examined for ocular complications. The prevalence of macular degeneration and cataract was 24.3%, which did not differ substantially from previous reports in older control populations. One patient was found to have angioid streaks. These findings suggest that the prevalence of serious ocular complications of Paget's disease is not as high as previously reported.—Michael A. Kass

*Birmingham and Midland Eye Hospital, Church St., Birmingham B3 2NS, England.

The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shal-

low anterior chamber, and angle closure glaucoma. Pitts, J. F., and Jay, J. L.*: Br. J. Ophthalmol. 74:601, 1990.

FUCHS' CORNEAL DYSTROPHY, HYPERMETROPIA, SHALLOW ANTERIOR CHAMBER, ANGLE-CLOSURE GLAUCOMA

Twenty-four patients with Fuchs' corneal dystrophy were compared to a control group with respect to refractive error and ocular biometry. The mean spherical refractive error in the patients with Fuchs' dystrophy was +2.48 diopters as compared to −0.31 diopters for the control group. The mean axial length for the group with Fuchs' dystrophy was 22.1 mm as compared to 23.4 mm for the control group. The anterior chamber depth in the group with Fuchs' dystrophy was 2.2 mm as compared to 2.7 mm in the control group. Each of these differences was statistically significant. Five of the 24 patients (21%) with Fuchs' dystrophy had shallow anterior chambers and three (12%) had angle-closure glaucoma, which required peripheral iridectomy. Acute angle-closure glaucoma and Fuchs' dystrophy can be confused because of similar symptoms of pain, glare, halos, and blurring of vision. The increased risk of angle-closure glaucoma supports the widely accepted practice of combining penetrating keratoplasty with lens extraction in patients with Fuchs' corneal dystrophy.—Michael A. Kass

*Tennent Institute of Ophthalmology, University of Glasgow, Western Infirmary, 38 Church St., Glasgow G11 6NT, Great Britain.

The glaucoma laser trial (GLT). 2. Results of argon laser trabeculoplasty versus topical medicines. The Glaucoma Laser Trial Research Group*: Ophthalmology 97:1403, 1990.

OPEN-ANGLE GLAUCOMA, ARGON LASER TRABECULOPLASTY

The Glaucoma Laser Trial, a multicenter, randomized clinical trial involving 271 patients, was designed to assess the efficacy and safety of argon laser trabeculoplasty as an alternative to treatment with topical medication for controlling intraocular pressure in patients with newly diagnosed, previously untreated, primary open-angle glaucoma. In each patient, one eye was randomly assigned to laser trabeculoplasty and the other eye was assigned to medical treatment with timolol maleate 0.5%. Medication was initiated or changed in both eyes according to the same stepped regimen when intraocular pressure was not controlled adequately. Throughout the two-year follow-up period, the laser-treated eyes had lower mean intraocular pressures than did the medically treated eyes by 1 to 2 mm Hg. Presumably, some portion of this differential was caused by a contralateral effect of medication given to the medically treated eyes. Fewer laser-treated eyes than medically treated eyes required simultaneous prescription of two or more medications to control intraocular pressure. After two years of follow-up the following results were found: 44% of the laser-treated eyes were controlled by argon laser trabeculoplasty alone, whereas 30% of the medically treated eyes were controlled by timolol alone; 89% of the laser-treated eyes and 66% of the medically treated eyes were controlled within the stepped medical regimen; and 56% of the laser-treated eyes required medical therapy to control intraocular pressure. There were no major differences between the two treatment groups with respect to changes in visual acuity or visual field over this follow-up period.—Michael A. Kass

*GLT Coordinating Center, Department of Epidemiology, Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD 21205.

Laser-induced occlusion of corneal blood vessels with variable emission and absorption. Jean, B.*, Thiel, H.-J., Maier, J., Kischkel, C., Baumann, M., and Bachmann, W.: Ophthalmologica 201:113, 1990.

CORNEAL NEOVASCULARIZATION, VESSEL OCCLUSION, DYE LASER, DYE-ENHANCED ABSORPTION

A number of investigators have attempted to occlude corneal vessels with laser energy. To limit side effects such as corneal burns, it is important to minimize laser energy. In this study, intravenous fluorescein was administered in an attempt to reduce the laser energy necessary to occlude corneal vessels. Corneal vessels with diameters less than 50 μm were occluded permanently in 43% of the patients who received intravenous fluorescein in contrast to 28% of the patients who did not. All treatments were performed using a dye laser.

Corneal vessels greater than 50 μm in diameter were occluded using the lowest energy levels when a wavelength of 575 nm was used. This wavelength approximates the absorption maximum of hemoglobin.—Michael A. Kass

*Universitäts-Augenklinik, Abteilung I, Schleichstrasse 12, D-7400 Tübingen 1, Germany.

Visual impairment in a rural Appalachian community. Prevalence and causes. Dana, M. R.*, Tielsch, J. M., Enger, C., Joyce, E., Santoli, J. M., and Taylor, H. R.: JAMA 264:2400, 1990.

VISUAL IMPAIRMENT, APPALACHIA, MACULAR DEGENERATION, CATARACT, TRAUMA, AMBLYOPIA

A population-based survey of 1136 subjects aged 40 years and older was conducted in a rural valley of Kentucky to determine the nature and extent of visual disability in an underserved area of rural America. Data on corrected visual acuity and ocular history, along with demographic, socioeconomic, and health care utilization parameters, were gathered. Those subjects with an acuity below 20/60 in either eye underwent a comprehensive ophthalmologic examination. The prevalence of binocular blindness (acuity worse than 20/400 in the better eye) was 0.44% and of monocular blindness (acuity worse than 20/400 in one eye) was 3.3%, approximately twice the national rates. The chief cause of bilateral visual impairment was macular degeneration among men and cataract among women. Cataract, trauma, and amblyopia were the major causes of monocular visual impairment in both sexes. Risk factor analysis revealed younger age, higher education, active employment, access to a health care facility, and comprehensive health insurance coverage to be inversely associated with visual impairment.—Authors' abstract

*Illinois Eye and Ear Infirmary, 1855 W. Taylor St., Chicago, IL 60612.

Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures. A prospective evaluation. Henderson, D. K.*, Fahey, B. J., Willy, M., Schmitt, J. M., Carey, K., Koziol, D. E., Lane, H. C., Fedio, J., and Saah, A. J.: Ann. Intern. Med. 113:740, 1990.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1, OCCUPATIONAL EXPOSURE OF HEALTH CARE WORKERS

A total of 1,344 clinical health care workers reported 179 percutaneous and 346 mucous membrane exposures to fluids from patients infected with human immunodeficiency virus type 1 during a six-year period. Additionally, 559 of these workers reported 2,712 cutaneous exposures to blood from patients infected with HIV-1 and more than 10,000 cutaneous exposures to blood from all patients during a 12-month period. Occupational transmission of HIV-1 occurred in a single worker after an accidental deep cut with a blood-contaminated sharp object. No infections occurred after either mucous membrane or cutaneous exposures to blood from patients infected with HIV-1. Combining the results of this study with other prospective studies, the risk for HIV-1 transmission associated with a percutaneous exposure to blood from a patient infected with HIV-1 is approximately 0.3% per exposure (95% confidence interval, 0.13% to 0.70%). The risks associated with occupational mucous membrane and cutaneous exposures are substantially smaller. These data support the use of barrier precautions and suggest a need for strategies that change health care providers' attitudes and behaviors.—Michael A. Kass

*Bldg. 10, Rm. 2C146, National Institute of Health, 9000 Rockville Pike, Bethesda, MD 20892.

Infection with human immunodeficiency virus type 1 (HIV-1) among recipients of antibody-positive blood donations. Donegan, E., Stuart, M., Niland, J. C., Sacks, H. S., Azen, S. P., Dietrich, S. L., Faucett, C., Fletcher, M. A., Kleinman, S. H., Operskalski, E. A., Perkins, H. A., Pindyck, J., Schiff, E. R., Stites, D. P., Tomasulo, P. A., Mosley, J. W.*, and the Transfusion Safety Group: Ann. Intern. Med. 113:733, 1990.

BLOOD RECIPIENTS, HUMAN IMMUNODEFICIENCY VIRUS TYPE 1

The authors retrospectively tested approximately 200,000 blood component specimens

stored in late 1984 and 1985 before tests for the human immunodeficiency virus were available. Recipients of HIV-1–positive specimens were then contacted and seen at three- to six-month intervals for up to four years for clinical and immunologic examination. One hundred thirty-three individuals received HIV-1–positive transfusions or other blood products. Nine of these individuals were excluded from the analysis because they had other possible exposures to HIV-1. Excluding these cases, 111 of 124 (89.5%) recipients were anti–HIV-1 positive. The type of blood component and the recipient's sex, age, and underlying condition did not influence the infection rates. The cumulative risk for developing the acquired immunodeficiency syndrome within 38 months after transfusion with HIV-1–positive material was 13%. By three years after the index transfusion, seropositive recipients had substantial alterations of their lymphocyte subsets. Thus transfusion of anti–HIV-1–positive blood infected 90% of recipients. The rate of progression to AIDS within the first 38 months after infection was similar to that reported for homosexual men and hemophiliacs.—Michael A. Kass

*University of Southern California, 1840 N. Soto St. (EDM 108), Los Angeles, CA 90032.

Loose connections between peer-reviewed clinical journals and clinical practice. Haynes, R. B.*: Ann. Intern. Med. 113:724, 1990.

MEDICAL JOURNALS, DISSEMINATION OF INFORMATION

Many important advances in medical care are first reported in the biomedical literature. Many physicians, however, are overwhelmed by the literature and are therefore unaware of the advances. The author believes that peer-review clinical journals impede the dissemination of validated advances to practitioners by mixing a few rigorous studies (communications from scientists to practitioners) with many preliminary investigations (communications from scientists to scientists). He advocates that journals wishing to improve communication with practitioners should feature rigorous studies of the nature, cause, prognosis, diagnosis, prevention, and treatment of disease and should feature sound clinical review articles. The author also advocates improving publication standards for clinical journals, providing more informative abstracts for clinical articles, fostering the development of derivative literature services, and enhancing practitioners' skills in critically appraising the medical literature.—Michael A. Kass

*Health Information Research Unit, Room 3H7, McMaster University Medical Center, 1200 Main St. W., Hamilton, Ontario, Canada L8N 3Z5.

Overall mortality and cancer mortality around French nuclear sites. Hill, C.*, and Laplanche, A.: Nature 347:755, 1990.

NUCLEAR REPROCESSING PLANTS, LEUKEMIA

Higher than expected mortality from leukemia has been observed in the population under age 25 living around Sellafield and Dounreay, nuclear reprocessing plants in the United Kingdom. We report the results of a similar study for the population residing around nuclear sites in France. The number of leukemia deaths was 58, comparable to the 62 in control areas, and slightly less than the 67 expected from national mortality statistics. Twelve deaths due to Hodgkin's disease were observed around nuclear sites; this is about twice the number of Hodgkin's deaths observed in control areas and twice the number expected from national mortality statistics. This observation must, however, be interpreted in light of the fact that several causes of deaths were studied, increasing the play of chance.—Authors' abstract

*Department of Biostatistics and Epidemiology, INSERM U287, Institut Gustave Roussy, 94805 Villejuif, France.

Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. Brown, G.*, Albers, J. J., Fisher, L. D., Schaefer, S. M., Lin, J.-T., Kaplan, C., Zhao, X.-Q., Bisson, B. D., Fitzpatrick, V. F., and Dodge, H. T.: N. Engl. J. Med. 323:1289, 1990.

CORONARY ARTERY DISEASE, CORONARY ARTERY ATHEROSCLEROSIS, LIPID-LOWERING THERAPY

It is unclear whether the progression of atherosclerosis can be retarded or reversed by reduc-

ing low-density lipoprotein cholesterol levels. One hundred forty-six men who had documented coronary artery disease, a family history of vascular disease, and apolipoprotein B levels greater than 125 mg/dl, were randomly assigned to one of three treatments. All patients received dietary counseling and Group 1 also received 20 mg of lovastatin twice a day and 10 g of colestipol three times daily. Group 2 received 1 g of niacin four times a day and 10 g of colestipol three times a day. Group 3 received placebo. The groups treated with lovastatin and colestipol and niacin and colestipol had substantial changes in the levels of both low-density lipoprotein and high-density lipoprotein. In the placebo group, 46% of the patients had definite progression of lesions in at least one of nine proximal coronary segments; regression of lesions was seen in 11% of patients. By comparison, progression was less frequent among the patients who received lovastatin and colestipol (21%) and those who received niacin and colestipol (25%), and regression was more frequent (lovastatin and colestipol, 32%; niacin and colestipol, 39%). Multivariate analysis indicated that a reduction in the level of apolipoprotein B and in systolic blood pressure and an increase in high-density lipoprotein cholesterol correlated independently with regression of coronary lesions. Noteworthy changes in clinical status (death, myocardial infarction, or revascularization for worsening symptoms) occurred in ten of 52 patients assigned to conventional therapy as compared with three of 46 assigned to receive lovastatin and colestipol and two of 48 assigned to receive niacin and colestipol. In men with coronary artery disease, intensive lipid-lowering therapy reduced the frequency of progression of coronary lesions, increased the frequency of regression, and reduced the incidence of cardiovascular complications.—Michael A. Kass

*Cardiology Division, RG-22, University of Washington, Seattle, WA 98195.

Three cases of EB virus–associated uveitis. Usui, M.*, and Sakai, J.: Int. Ophthalmol. 14:371, 1990.

EPSTEIN-BARR VIRUS, UVEITIS

Epstein-Barr virus, a DNA virus of the herpes group, has been strongly linked to Burkitt's lymphoma, nasopharyngeal carcinoma, infectious mononucleosis, and rheumatoid arthritis. Three patients with uveitis who were otherwise healthy and had no evidence of infectious mononucleosis were examined. All the patients had an upper respiratory prodrome and then developed severe bilateral anterior uveitis a few weeks later. The patients also had marked hyperemia and edema of the optic disks but little vitreous inflammation. The patients responded well to systemic corticosteroids, but recurrences were common. Paracentesis of the anterior chamber was performed in all three patients and increased titers to Epstein-Barr virus capsid antigen were found. In contrast, 37 patients with cataract and 14 patients with other types of uveitis all lacked antibodies to Epstein-Barr virus in the aqueous humor.—Michael A. Kass

*Tokyo Medical College Hospital, Nishishinjuku, Shinjuku-ku, Tokyo, Japan.

Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome. Structure and function. Cryotherapy for Retinopathy of Prematurity Cooperative Group*: Arch. Ophthalmol. 108:1408, 1990.

RETINOPATHY OF PREMATURITY, CRYOTHERAPY

This study of the safety and efficacy of cryotherapy in treating severe retinopathy of prematurity registered 9751 infants with birth weights less than 1251 g at 23 study centers. Two hundred ninety-one infants developed a defined threshold retinopathy of prematurity, and cryotherapy was performed in approximately half of the eyes through a randomization protocol. Twelve months after randomization, results of masked grading of fundus photographs of the posterior pole were similar to results obtained 3 months after randomization, and indicated an unfavorable outcome in 25.7% of the eyes that received cryotherapy compared with 47.4% of the control eyes ($P < .0001$). For the first time, masked Teller Acuity Card assessment of grating acuity was performed in this study group and indicated an unfavorable functional outcome in 35.0% of the treated eyes compared with 56.3% of the control eyes ($P < .0001$). These results indicate that cryotherapy reduces the risk of unfavorable

retinal and functional outcome from threshold retinopathy of prematurity.—Authors' abstract

*CRYO-ROP Headquarters, Department of Ophthalmology L467, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Rd., Portland, OR 97201.

Relationship of drusen and abnormalities of the retinal pigment epithelium to the prognosis of neovascular macular degeneration. Bressler, S. B.*, Maguire, M. G., Bressler, N. M., Fine, S. L., and the Macular Photocoagulation Study Group: Arch. Ophthalmol. 108:1442, 1990.

MACULAR DEGENERATION, RISK FACTORS FOR NEOVASCULAR MEMBRANES, LARGE DRUSEN, FOCAL HYPERPIGMENTATION OF THE RETINAL PIGMENT EPITHELIUM

We graded macular features of 127 fellow eyes of participants in the Macular Photocoagulation Study who had an extrafoveal choroidal neovascular membrane secondary to age-related macular degeneration in the first eye and no initial evidence of the neovascular form of age-related macular degeneration in the fellow eye. Our aims were to determine the relationship of drusen characteristics and retinal pigment epithelial abnormalities to the risk of subsequent development of neovascularization in the fellow eye and the risk of subsequent development of recurrent neovascular membranes after photocoagulation in the first eye. Regression analysis demonstrated that the presence of large drusen and focal hyperpigmentation of the retinal pigment epithelium were independent risk factors for the subsequent development of neovascularization in the fellow eye (relative risk, 2.4 and 2.5, respectively). Only 10% of eyes with no large drusen or any retinal pigment epithelial hyperpigmentation compared with 58% of eyes with both large drusen and retinal pigment epithelial hyperpigmentation developed neovascularization in the fellow eye within 5 years. Using multivariate Cox regression analysis, we noted that the risk of developing recurrent neovascular membranes in the first eye was significantly increased when large drusen (relative risk, 2.8) were noted in the fellow eye at the time of laser treatment in the first eye. Fundus features in the fellow eye appear to help identify patients at high risk of developing visual loss from recurrent neovascular membranes following laser treatment in the first eye and from development of a neovascular membrane in the fellow eye.—Authors' abstract

*Ste. 900, 550 N. Broadway, Baltimore, MD 21205.

Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs. Pournaras, C. J.*, Tsacopoulos, M., Strommer, K., Gilodi, N., and Leuenberger, P. M.: Ophthalmology 97:1329, 1990.

RETINAL ISCHEMIA, BRANCH VEIN OCCLUSION, RETINAL PHOTOCOAGULATION

Argon laser photocoagulation is used to treat a variety of ischemic diseases of the retina. It is unclear why photocoagulation is helpful in these conditions, although one common theory is that photocoagulation destroys portions of the retinal pigment epithelium and retina, which allows oxygen to diffuse from the choroid to the inner retina. The authors used an argon laser to produce superotemporal branch vein occlusions at the first bifurcation in miniature pigs. Three weeks later these animals were noted to have ischemic vasoproliferative retinal microangiopathy as confirmed by fluorescein angiography and fundus photography. A subset of the animals then underwent argon laser scatter photocoagulation in the ischemic retinal zones. The variables of treatment were spot size of 250 μm, exposure time of 0.1 millisecond, and power of 150 to 250 mW. The power was adjusted to produce a visible whitening in the deep retinal layers. Preretinal partial pressure oxygen measurements were made using oxygen-sensitive microelectrodes. The normal preretinal partial pressure of oxygen is 27.3 ± 2.9 mm Hg. Five weeks after experimental branch vein occlusion, the preretinal partial pressure oxygen level was 13.7 ± 1.1 mm Hg in the nontreated areas and 28.0 ± 3.0 mm Hg in the treated areas. Thus scatter photocoagulation of the ischemic retinal areas returned local preretinal partial pressure of oxygen to physiologic levels.—Michael A. Kass

*University Eye Clinic, 22 rue Alcide-Jentzer, 1211 Genève 4, Switzerland.

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
435 N. Michigan Ave., Suite 1415
Chicago, IL 60611

The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

National Eye Institute: 12th Annual Clinical Vision Research Course

The National Eye Institute will hold its 12th Annual Clinical Vision Research Course, Clinical Vision Research—Epidemiologic and Biostatistical Approaches, at the Longboat Key Club in Longboat Key, Florida, April 24–27, 1991. For further information, write Christine Stewart, Stewart International, Ltd., 87-91 Boylston St., Brookline, MA 02146; telephone (617) 738-1575 or (800) 441-8666.

German Ophthalmological Society: International Symposium—Update on Infectious Diseases of the Eye

The German Ophthalmological Society will hold an international symposium, Update on Infectious Diseases of the Eye, Sept. 19–21, 1991, in Bonn-Köln, Germany. For further information, write Alexander A. Bialasiewicz, M.D., University Eye Hospital Bonn, Sigmund Freud Str. 25, 53 Bonn 1, Germany.

The Fourth International Cataract, Implant, Microsurgical and Refractive Keratoplasty Meeting

The Fourth International Cataract, Implant, Microsurgical and Refractive Keratoplasty Meeting will be held at the Intercontinental Hotel in Seoul, Korea, May 8–10, 1991. For further information, write Jae Ho Kim, M.D., Department of Ophthalmology, Kangnam St. Mary's Hospital, Catholic University Medical College, 505, Banpo-dong, Seocho-ku, Seoul 137-040, Korea; telephone 82-2-593-5141 (ext. 1335); Fax 82-2-533-6718.

First World Congress of Medical Polonia

The First World Congress of Medical Polonia (physicians of Polish extraction) will be held June 19–23, 1991, in Czestochowa, Poland. Foreign physicians are welcome. For further information, write Krzysztof Muskalski, M.D., First World Congress of Medical Polonia, Dr. Rydygier's Surgical Hospital, ul. Mirowska 25, 42-200 Czestochowa, Poland.

The Johns Hopkins Medical Institutions: Design and Analysis Issues in Clinical Trials

The Johns Hopkins Institutions will sponsor a course, Design and Analysis Issues in Clinical Trials, June 13 and 14, 1991. For further information, write the Program Coordinator, Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Bldg., 720 Rutland Ave., Baltimore, MD 21205; telephone (301) 955-2959.

Lenox Hill Hospital: Phacoemulsification Course

Lenox Hill Hospital will sponsor a course, Phacoemulsification, April 26, 1991, at the New York Helmsley Hotel. An additional course, Phacoemulsification Wet Lab, will be held April 27, 1991, at the hospital. For further information, write Gabrielle Coren, Department of Ophthalmology, Lenox Hill Hospital, 100 E. 77th St., New York, NY 10021; telephone (212) 439-2385.

Long Island Jewish Medical Center and North Shore University Medical Center: A Clinical Day in Ophthalmology—Medical Retina

The Long Island Jewish Medical Center and North Shore University Medical Center will

sponsor a clinical day in ophthalmology, Medical Retina, at the Holiday Inn Crowne Plaza (LaGuardia Airport), East Elmhurst, New York, March 27, 1991. For additional information, write Ann J. Boehme, CMP, Continuing Education Coordinator, Long Island Jewish Medical Center, New Hyde Park, NY 11042; telephone (718) 470-8650.

Lyme Borreliosis Foundation: Unlocking the Pathogenesis of *Borrelia burgdorferi* and Implications for Patient Management

The Lyme Borreliosis Foundation, headquartered in Tolland, Connecticut, and the UCLA Department of Continuing Education in Health Sciences will cosponsor a conference, Unlocking the Pathogenesis of *Borrelia burgdorferi* and Implications for Patient Management, April 26 and 27, 1991, at the Guest Quarters Hotel in Santa Monica, California. For additional information, write Lori Chaponis, R.N., Lyme Borreliosis Foundation, P.O. Box 403, Tolland, CT 06084; telephone (203) 871-2900.

Manhattan Eye, Ear and Throat Hospital: Contact B- and A-Scan Ultrasonography for the Clinician

The Manhattan Eye, Ear and Throat Hospital will sponsor a course, Contact B- and A-Scan Ultrasonography for the Clinician, April 6, 1991, in New York City. Yale L. Fisher, M.D., is the course director. For additional information, write Kimberly Corbin, Course Coordinator, Department of Ophthalmology, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021; telephone (212) 605-3761.

Medical College of Wisconsin: Current Concepts in Ophthalmology

The Medical College of Wisconsin will sponsor a course, Current Concepts in Ophthalmology, June 7–9, 1991, at The American Club in Kohler, Wisconsin. For further information, write Gary Abrams, M.D., Eye Institute, Medical College of Wisconsin, 8700 W. Wisconsin Ave., Milwaukee, WI 53226; telephone (414) 257-5353.

Rochester Eye Institute: 15th Annual Seminar

The Rochester Eye Institute will conduct its 15th Annual Seminar at the Rochester Riverside Convention Center June 13 and 14, 1991. For further information, write Catherine Sgabellone, R.N., Rochester Eye Institute, 919 Westfall Rd., Rochester, NY 14618; telephone (716) 461-8427.

The American Society of Ophthalmic Plastic and Reconstructive Surgery: 1991 Officers

The new officers of The American Society of Ophthalmic Plastic and Reconstructive Surgery, Inc., for 1991 are president, Arthur S. Grove, Jr., succeeding Bernice Z. Brown. The vice-president is Albert Hornblass, succeeding John A. Burns. The treasurer is Gerald J. Harris, succeeding George L. Paris. The secretary is John N. Harrington, succeeding William R. Nunery. The program chairman is Bradley N. Lemke, succeeding Paul T. Gavaris. John A. Burns was named president-elect, succeeding Arthur S. Grove. The executive secretary is Daniel L. McLachlan, 111 N. Wabash St., Chicago, IL 60602.

Pan-American Association of Ophthalmology: 1991 Officers

Robert C. Drews, of Clayton, Missouri, succeeded Enrique Malbrán, of Buenos Aires, Argentina, as president of the Pan-American Association of Ophthalmology. Francisco Contreras, of Lima, Peru, was named president-elect; Alice McPherson, of Houston, Texas, is vice-president; Paul Lichter, of Ann Arbor, Michigan, is secretary-treasurer for the English language. Francisco Martinez Castro, of Mexico City, Mexico, is secretary-treasurer for the Spanish language, and Rubens Belfort, of São Paulo, Brazil, is secretary-treasurer for the Portuguese language.

11th Clement McCulloch Lecture

Dr. Henk Sperkreijse, professor and director of the Dutch Interuniversity Eye Institute of Amsterdam, Netherlands, will give the 11th Clement McCulloch Lecture, April 5, 1991, in Toronto, Ontario, Canada. The Lecture will be

given during the 33rd annual departmental research meeting of the Department of Ophthalmology, University of Toronto. For further information, write G. E. Trope, M.D., Department of Ophthalmology, Toronto General Hospital, Eaton Bldg., 5-306, Toronto, Ontario, M5G 2C4, Canada.

Minnesota Academy of Ophthalmology: 22nd Annual William L. Benedict Lecture

The Minnesota Academy of Ophthalmology presented the 22nd Annual William L. Benedict Memorial Lecture at its meeting Jan. 11, 1991. Robert L. Herbst, president of the Lake Superior Center in Duluth, Minnesota, was the guest speaker. Dr. Benedict was president of the Ophthalmic Publishing Company at the time of his death in 1969.

Personal

John L. Wobig

John L. Wobig has been appointed the first recipient of the Lester T. Jones Endowed Professorship in Ophthalmic Plastic and Reconstructive Surgery at the Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon. The chair was established in 1990 in honor of Lester T. Jones, M.D., a founding father of lacrimal and reconstructive surgery. Dr. Wobig was on the clinical faculty of the Oregon Health Sciences University before accepting the full-time position as director of the Ophthalmic Plastic and Reconstructive Surgery Service.

THE DRY EYE SPECIALISTS

Presenting our growing family of Eagle Vision-Freeman™

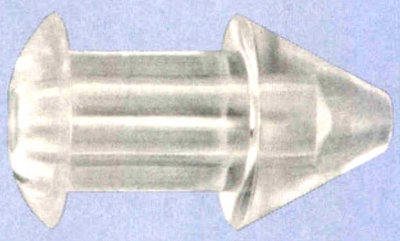
PUNCTUM PLUGS

U.S. Patent No. 3,949,750
Dilator/Inserter Des. No. 295,445

MEDIUM SIZE No. 0003
Improved nose design for easier insertion — 2.0mm Length

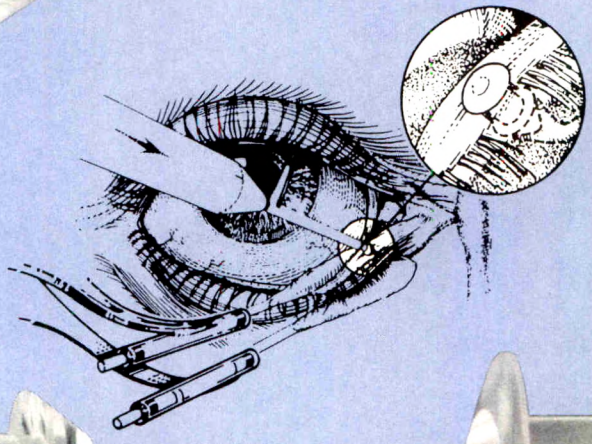
STANDARD SIZE No. 0001
2.8mm Length
The original plug



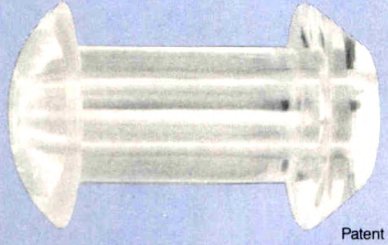


SMALL SIZE No. 0004
1.6mm Length
Reduced dome height and width to facilitate insertion—1.6mm Length



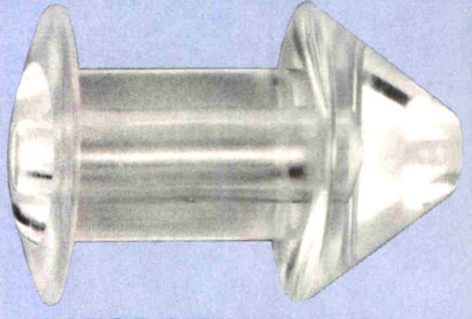


Introduction of punctum plug held in place by inserter end of dilator/inserter instrument, using Lid Fixation Forceps.



Patent No. 4,915,684

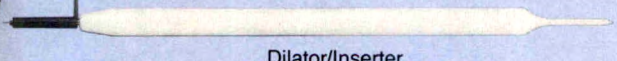
PUNCTUM FLOW CONTROLLER No. 0008
Standard Size Plug with open nose to modulate the flow of lacrimal fluid through a punctum and canaliculus—2.3mm Length.



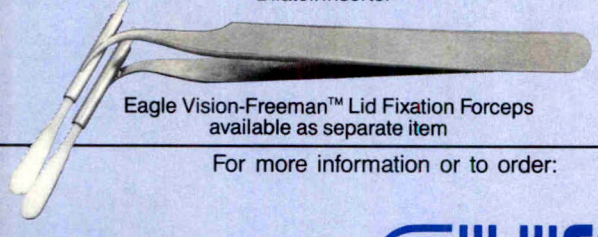
LARGE SIZE No. 0009
25% wider diameter than Standard Size Plug for patients with lax lids and large puncta, featuring Medium Size Plug dome—2.8mm Length.

EACH KIT CONTAINS:

2-Punctum Plugs of medical grade silicone
1-Dilator/inserter combination instrument
Physician instructions

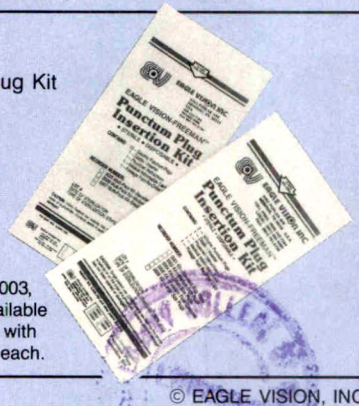


Dilator/Inserter



Eagle Vision-Freeman™ Lid Fixation Forceps available as separate item

Punctum Plug Kit



Products #0001, #0003, and #0004 also available **MULTI-PACK KITS** with 10 Punctum Plugs each.

For more information or to order:

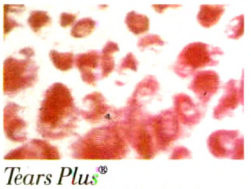
© EAGLE VISION, INC. 1990

EAGLE VISION™
6263 POPLAR AVE., SUITE 650, MEMPHIS, TN 38119
(800) 222-7584 • (901) 682-9400 • FAX (901) 761-5736

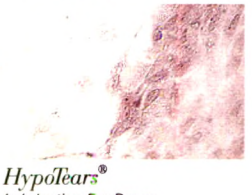
THE FORMULATION IS

MILD

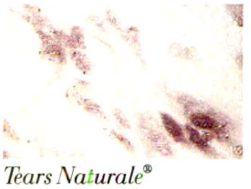
Human Corneal Epithelial Cells
After Constant Immersion
For Six Minutes
(In Vitro - 400X Magnification.
Clinical Significance Is Unknown)[1]



Tears Plus®
Lubricant Ophthalmic Solution
- *Normal cell morphology as shown by retention of neutral red dye.*



HypoTears®
Lubricating Eye Drops
- *Disrupted cell and lysosomal membranes as evidenced by loss of neutral red dye from lysosomes.*



Tears Naturale®
Lubricant Eye Drops
- *Disrupted cell and lysosomal membranes as evidenced by loss of neutral red dye from lysosomes.*



A comfortable, multidose tear with the relative safety of chlorobutanol. Unlike other preservatives used in some artificial tears, chlorobutanol is not cytotoxic to the surface epithelium[2] and does not adversely affect the lipid layer, as demonstrated by in vivo and in vitro studies.[3]

And that's comforting news for your mild dry eye patients who use tear supplements up to four times daily.



Tears Plus Solution.
Comfortable, convenient and mild.

Tears Plus® Lubricant Ophthalmic Solution

Available in 15 mL and 30 mL multidose bottles.

STAGE 1
IN THE SYSTEM FOR OCULAR SURFACE DISEASE™

A Rational Plan To Manage Dry Eye Associated With Ocular Surface Disease

ALLERGAN PHARMACEUTICALS
Allergan Pharmaceuticals
A Division of Allergan, Inc.
Irvine, CA 92713 ©1991 Allergan, Inc.

1. Data on file, Allergan, Inc.
2. Pfister RR, Burstein N. The effects of ophthalmic drugs, vehicles and preservatives on corneal epithelium: a scanning electron microscope study. Investigative Ophthalmology 1976;15:246.
3. Holly FJ. Surface chemical evaluation of artificial tears and their ingredients. 11. Interaction with a superficial lipid layer. Contact Lens 1978 July/Sept;4(3):52-68.

Tears Naturale® and HypoTears® are registered trademarks of other companies.